Neurology

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[1] *U.S. Armed Forces Med. Journal, September, 1950*

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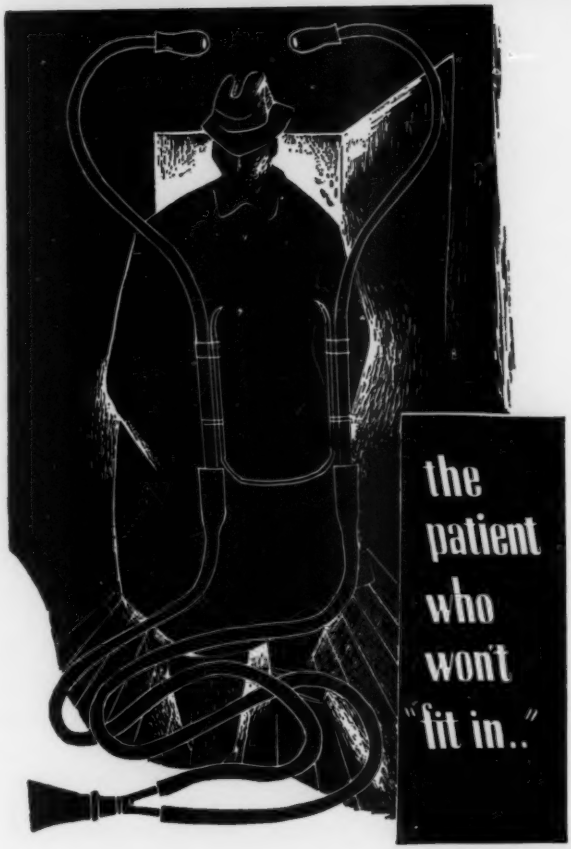

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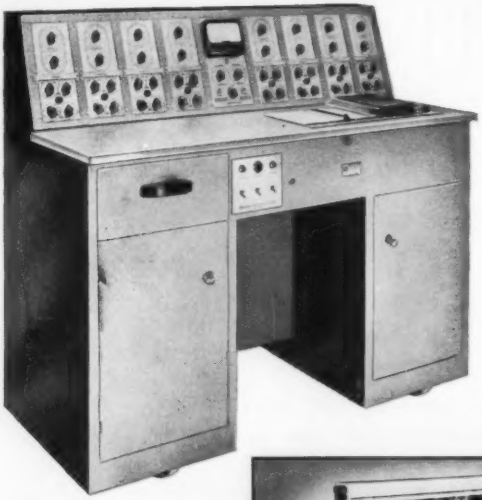

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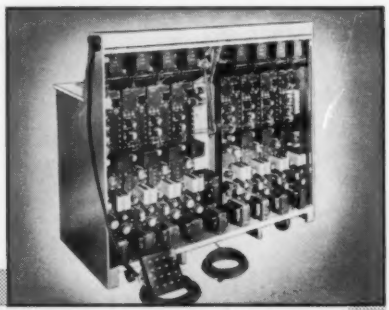

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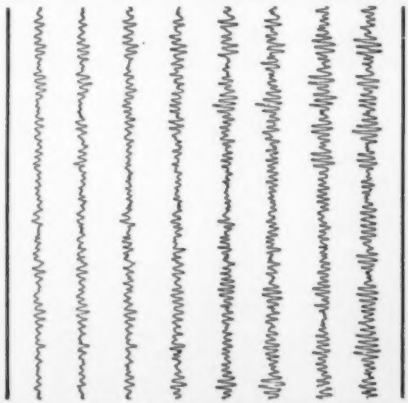

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

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Neurology

Gliomas Involving the Splenium of the Corpus Callosum

Benno Schlesinger, M.D.

WHILE gliomas confined to the splenium of the corpus callosum are exceedingly rare, those spreading into the forceps major on either side appear to be somewhat more common. The series of 20 neoplasms verified at autopsy which form the basis of this report includes not only lesions of the splenium and the forceps major, but also gliomas which cross the midline in the region of the posterior portion of the corpus callosum. Seventeen cases of this series were collected from the literature. One of these lesions was classified histologically as oligodendroglioma, another neoplasm as fibrillary astrocytoma; the remaining cases were either multiform spongioblastomas or were considered to be highly cellular gliomas.

The present study is undertaken in the hope that symptoms due to involvement of the splenium may be distinguished from distant and neighboring effects by a comparison of the various clinical manifestations and a correlation of clinical and surgical experiences.

According to Ostertag,[32] gliomas of the splenium, like other gliomas of the corpus callosum, originate in the region of the superomedial angle of the lateral ventricle. Further growth of the lesion is either systematized or irregular. Systematized growth takes place along the fibers of the corpus callosum, commissura hippocampi and fornix, which may become

From the neurosurgical services of the Mount Sinai and Bronx Hospitals, New York, N.Y.

The roentgenologic features of the cases under study have been reported in a separate article (Schlesinger, B., J. Neurosurg. 7:351, 1950).

markedly thickened. Early infiltration of the cingular gyri appears to be the rule. Unsystematized growth may involve the thalamus, the caudate nucleus and the choroid plexus of the lateral ventricles. Sooner or later lesions may infiltrate most of the posterior portion of both cerebral hemispheres, tumefaction of the splenium being a common property of the entire group.

The distribution of lesions as seen at autopsy is indicated in figure 1. Our three previously unpublished cases are reported in full.

A comparison of large numbers of neoplasms is facilitated by the following classification of neurologic and other abnormalities found useful by the author[39] on a previous occasion.

1. Mental changes
2. Frontal lobe signs, and signs due to involvement of the olfactory nerves and optic chiasm
3. Basal ganglia signs
4. Thalamic signs
5. Hypothalamic and pituitary signs
6. Sensory-motor signs
7. Temporo-parieto-occipital signs (including those due to optic radiation involvement)
8. Brain stem signs
9. Cranial nerve signs
10. Cerebellar signs
11. Signs of intracranial hypertension
12. Physical and systemic signs suggestive of intracranial lesions
13. Laboratory and cerebrospinal fluid findings
14. Non-classifiable neurologic disturbances
15. Miscellaneous (developmental trend of the disease, age and sex incidence, etc.)

CLINICAL FINDINGS IN THREE PERSONALLY OBSERVED CASES

Case 1. (Serial Number XII)—R.R., a 44 year old male, was first observed in September 1934. His wife stated that he had been suffering from unsteadiness of gait, failing vision, double vision, episodes of left sided weakness, difficulties in urination and headaches for an unspecified period of time.

The general physical examination was negative. The neurologic examination revealed loss of memory; lack of spatial and defective temporal orientation; left sided hyposmia; left sided paresis and hemihypesthesia for both superficial and deep qualities; increased deep reflexes; hypotonicity in the upper extremity; absent abdominal and cremasteric reflexes; a positive ankle clonus and Babinski sign; bilateral choked disk, measuring between three and four diopters.

At operation a glioma occupying the depth of the left parietal lobe was found. Autopsy revealed spread of the lesion into the opposite hemisphere through the splenium of the corpus callosum.

Case 2. (Serial Number XIX)—S.H., a 72 year old woman, developed memory defects, most pronounced for recent events, and episodes of disorientation and confusion one year prior to admission to the hospital on March 25, 1948. She had also become subject to occasional periods of irritability and depression. According to her son, from whom the history was obtained, she was confused one week before hospitalization. The patient herself complained of general weakness and dizziness, and gradually found it impossible to walk unaided.

The physical examination was non-contributory.

The neurologic examination revealed the following positive findings: marked difficulties in handling abstract concepts; disorientation as to time and place; agraphia; acalculia; left right disorientation; ideokinetic apraxia; nominal aphasia; inability to

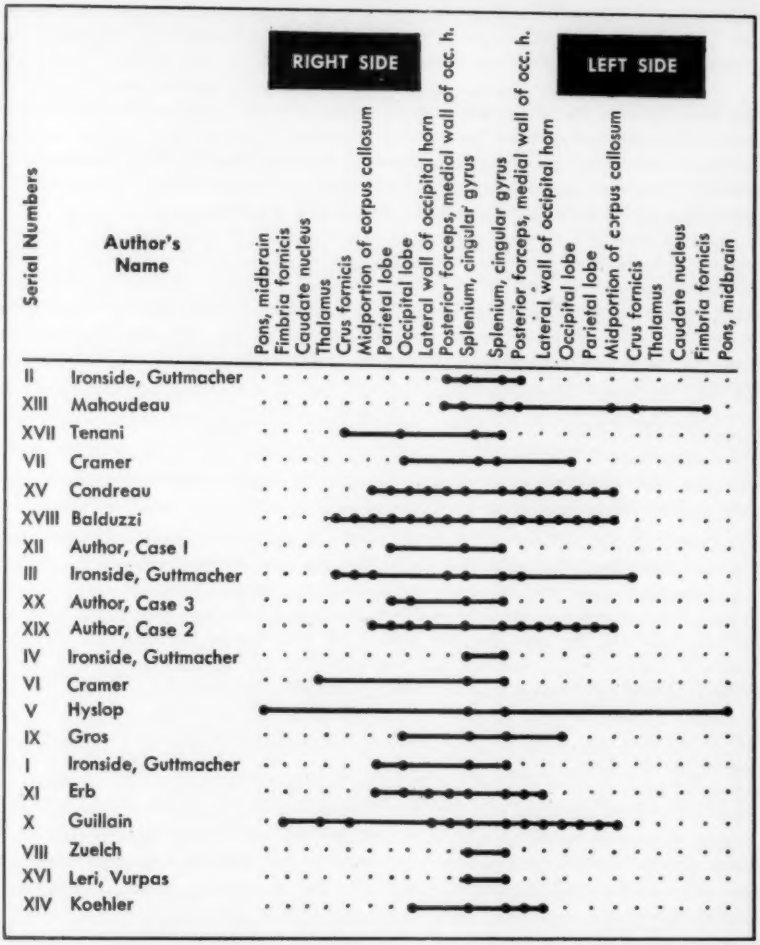

FIG. 1. Involvement of the brain by spread of gliomas of the splenium of the corpus callosum. Large dots indicate presence and small dots, absence of involvement of various anatomical structures. Each horizontal line represents one case.

select designated items from a group of objects; and marked perseveration tendency in naming objects. There were, however, no difficulties in oral repetition and the patient was able to carry out some extremely simple commands.

The first electroencephalogram, taken on admission, was normal. Lumbar puncture revealed an initial pressure of 246 mm. which fell to 140 mm. following removal of 10 cc. of clear, slightly xanthochromic cerebrospinal fluid. The total protein content

was 280 mg. per cent. There were 88 white cells, all lymphocytes, and 14 crenated red cells per cu. mm. The Wassermann and colloidal gold reactions were negative; the globulin reaction, positive.

Following lumbar air injection the electroencephalogram showed general dysfunction accentuated in the left parieto-occipital region, and dysfunction of the diencephalic centers. Aphasia became more pronounced following this procedure, and the patient developed a bilateral grasp reflex, a bilateral Babinski sign and papilledema. She gradually became stuporous, incontinent and developed nuchal rigidity. Eventually, a left hemiparesis developed. She died six weeks after admission.

Autopsy showed a moderate degree of arteriosclerosis of the blood vessels at the base of the brain. Both hemispheres were flabby and the convolutions slightly flattened. Palpation revealed an area of definitely decreased resistance occupying the right upper parietal region. There was evidence of mild bilateral pressure cone formation in both the region of the uncus and the cerebellar tonsils. On sectioning the brain an enormous tumor mass was found involving the posteromedial segment of both cerebral hemispheres. It extended from about the beginning of the crura of the fornix backward, replacing the white matter almost completely and undermining the gray matter. The tumor was hemorrhagic, and needle tracts could be seen clearly in the disintegrating tumor tissue close to the atrium of the left lateral ventricle. The anterior horns of the lateral ventricles were moderately and symmetrically dilated, their bodies narrow and their posterior horns reduced to slit-like cavities.

Case 3. (Serial Number XX)—N.L., a 53 year old woman, was admitted to the hospital on September 24, 1948. Her family reported that she had been a little strange for a long time, apparently due to extreme absentmindedness. Nine days prior to admission it was noted that she was unable to remember what was said to her or what she had done. On the same day the patient fell suddenly to the floor, but did not lose consciousness. Since then she had been suffering from increasingly severe, intermittent unlocalized headaches and vomiting, difficulties in concentration and loss of memory for recent events.

The general physical examination was non-contributory. The neurological examination revealed some apathy; defective appreciation of time and space relationships; defects of memory with a slight tendency to confabulation and jocosity; a bilateral grasp reflex, more pronounced on the left side; generally hyperactive tendon reflexes; diminished response to stimuli applied to the right side of her body; reduced voluntary motor activity on the right; generally increased tendon reflexes; a bilateral Babinski sign and a positive right Oppenheim sign; difficulties in naming objects and in reading figures; inability to calculate simple tests; inability to write mathematical symbols; apractic difficulties in performing with the mimic musculature and fingers. The tests could not be improved by repetition. There was some tendency to repetitive speech, the aphasic disturbances increasing during the patient's stay in the hospital. There was inequality of the pupils, the left being slightly larger; an absent light reflex on the left; intermittent ptosis on the left; external and internal ophthalmoplegia. Later, the right pupil also became fixed to light and dilated. Another sign of midbrain involvement was the paroxysmal hypotonia in the lower extremities, noted in the history. Signs of intracranial hypertension included a slightly positive Kernig sign, a pulse rate of 56, and blurring and large hemorrhages in the left optic disk and fundus on that side.

At operation the atrium of the right lateral ventricle was opened and the wall of the ventricle found to be pathologically altered. No tumor tissue was removed. At

autopsy the choroid plexuses of the lateral ventricles were displaced laterally by a soft fleshy pinkish white tumor mass which incorporated the entire splenium of the corpus callosum, more so on the right. The neoplasm extended into the frontoparietal region and as far caudad as the parietooccipital junction. On microscopic examination the tumor showed the structure of a highly cellular glioma.

COMPARATIVE STUDY OF A SERIES OF TWENTY CASES

1. *Mental changes* were a constant feature, the type of disturbance having been specified in all but one case. Disturbances in intellect were present in 16 cases (84 per cent), disturbances in affect, behaviour and personality in 10 (52 per cent), and disturbances in consciousness in nine (47 per cent).

Although a very high incidence of psychiatric manifestations in tumors of the corpus callosum, including the splenium, has been noted by various observers, it is remarkable that mental changes occurred not only in every one of this series, but also appeared in the inaugural phases of the disease. These observations are puzzling in view of the fact that surgical section of the entire corpus callosum does not give rise to any deterioration of higher mental functions. According to Critchley,[9] occlusion of the main stem of the anterior cerebral artery produces definite mental disturbances which may amount to actual dementia. In these cases, however, softening involves not only the anterior seven-eighths of the corpus callosum but, in addition, a large portion of the cerebral hemisphere.

The available evidence suggests therefore that (a) the mental changes are due to involvement of neighboring structures, as already suspected by Gowers;[15] (b) that one cerebral hemisphere, in any case the dominant one, represents an independent unit; and (c) as a corollary, that the callosal fibers, as far as higher mental functions are concerned, belong to the least important fiber systems of the neopallium.

It is significant that the incidence of mental changes is at its peak not only in neoplasms of the genu of the corpus callosum, which connects the anterior association fields of either side, but also in those of the splenium, which links the posterior association fields in a similar fashion, while psychiatric manifestations are relatively rare in tumors of the midportion of the corpus callosum which connects chiefly the sensory-motor regions.[41]

In a series of 14 midcallosal tumors, mental disturbances were observed in eight cases (57 per cent), intellectual disturbances in seven cases (50 per cent), and disturbances in affect in four cases (28 per cent). There were no disturbances in consciousness.[41]

Further, it is of importance that mental changes due to implication

of the anterior differ from those of the posterior areas. Disturbances in memory are more common in tumors of the splenium, while some affective disturbances, particularly lack of drive and euphoria, are more frequently encountered in tumors of the rostrum and genu.[41]

The significance of these findings can be best appreciated by an evaluation of certain anatomic and physiologic facts which were, in part, anticipated by some of the early writers.

Both Jackson[22] and Betz[3] postulated that the anterior part of each cerebral hemisphere subserves motor functions and the posterior, sensory functions, the same idea having been re-emphasized by Kleist[23] in a somewhat more elaborate fashion. However, these concepts have never been specified in anatomic terms, nor could they possibly have been validated at that time by more recent clinical and rapidly accumulating neurophysiologic experiences.

Jackson spoke of the frontal lobes as the highest motor, and the "occipital lobes as the highest sensory centers of the cerebral subsystem of the three levels . . . It is to be understood that the unit of the whole nervous system is sensory-motor, and also that the so called motor provinces of the middle and highest levels at least, are supposed to be only chiefly motor, and the sensory provinces only chiefly sensory."* Kleist believes that thought processes have both sensory and motor aspects. Intellectual function is a dual entity (Doppelwesen), comprising both sensory and motor elements. Similar views were advanced by Wechsler[48, 49] with reference to speech and its dysfunctions.

Since Jackson formulated his concept of sensory-motor dualism permeating all levels of the central nervous system, including the intellectual, some of the following facts which have important implications for the problem under discussion have been brought to light.

In terms of comparative anatomy, the anterior association fields are an outgrowth of the precentral, the posterior of the postcentral gyrus and the other primary neocortical centers of sense organs.[31] Morphologic investigations have shown that the central sulcus of the Island of Reil represents an extension of the rolandic fissure. Therefore, the anterior part of the Island of Reil belongs to the frontal, the posterior to the parietal lobe.[11, 17] Thus, the boundary line between the anterior and the posterior part of the cerebral hemisphere in the sense of Jackson and Betz is the rolandic fissure and its extensions toward the anterior perforated space. This pattern is completed by the extension of the electrical-

*According to Hughlings Jackson[45] the lowest level extends from the conus medullaris to the tuber cinereum, the middle level to the sensory-motor region and the corpus striatum, and the highest to the highest motor and sensory cortical centers.

ly excitable motor cortex into the depth of the interhemispheric fissure, where it closely approaches the superior surface of the corpus callosum. Cytoarchitectonic studies which traced Betz cells as far as the midportion of the cingular gyrus[3] have added weight to the work of the neurophysiologists.

Although overlapping in part, the subcortical connections of the two cortical territories or superstructures of the sensory-motor areas are also different. The "prerolandic" segment of the cerebral hemisphere, comprising the part of the brain lying between the rolandic fissure and its extensions on the one hand, and the frontal pole on the other, is connected with the association nuclei of the thalamus, (N. medialis and anterior); the greater "postrolandic" segment of the cerebral hemisphere, which includes its remaining portion, is linked to the relay nuclei of the thalamus, (N. lateralis, corp. geniculatum mediale and laterale).* The posterior association fields receive, therefore, the inflow ultimately derived from the sense organs via relay nuclei and the primary neocortical centers; the anterior association areas, in spite of their motor character, the autonomic inflow from the hypothalamus via dorsomedial and anterior nuclei.[5, 6] They are connected with the posterior association fields by the fasciculus cinguli, uncinnatus and arcuatus.[37]

The posterior association fields, whose relative and absolute growth in man surpasses that of the frontal areas,[4] are concerned not only with the reception of stimuli that flow in from the sense organs, but also with the formation of engrams and their elaboration to higher mental functions.[33] Reinstatement of sensations or at least their relevant residues, and re-experience of more complex mental activities are mnestic functions which, while taking place on a functionally higher plane than impressions, have clearly sensory characteristics.

The anterior association fields which, by virtue of some of their subcortical fiber connections, are to be regarded as cortical provinces of the autonomic nervous system—notwithstanding of course their role as integrative center of other activities (eye movements, equilibrium, posture, etc.)—maintain a homeostatic level of receptivity which fluctuates in adaptation to demands. Inattention and distractibility, for instance, the forced replacement of adaptive by reflex-like behaviour so often encountered in frontal lobe lesions, are manifestations of lowered receptivity

*With rise in the phylogenetic scale the ventrolateral nucleus of the dorsal thalamus acquires increasingly extensive connections with the rostral portion of the frontal lobe.[24, 38, 47] That a similar developmental trend exists with reference to the medial nucleus of the thalamus and the basitemporal region is suggested by some work which antedated the modern physiologic and experimental approach in neuroanatomy.[10, 35] These phylogenetic "addenda" however do not alter the basic pattern of thalamocortical relations.

of the posterior association fields, while concentration or dominance of intended behaviour favors both initiation and conclusion of thought processes. The results of psychosurgical procedures, among other observations, suggest that emotional and instinctual forces whose relationship to the diencephalon is well known, enter the play of cortical activity at the frontal end of the intellectual plane as important motivational elements, codetermining trends of thought and action. These observations validate the concept that the anterior association fields have both stimulatory and inhibitory functions.

It is realized that this concept deprives the frontal lobes of their role as "the" organ of the mind and demotes them to agents of the diencephalon. It is, therefore, not surprising that impairment of frontal lobe function, at least in the physiologic sphere under consideration, follows the derangement pattern of a homeostatic mechanism. We may find both mental sluggishness and overproductivity (the latter in terms of energy spent rather than of quality); euphoria and depression; distractibility and undue tenacity of attention.[42] Diencephalic dysfunction may produce, among other disturbances, emaciation and obesity; distaste for food and insatiable appetite; precocious puberty and hyposexualism;[31] increased desire to sleep and agrypnia; and psychomotor hypoactivity as well as hyperactivity.[44] While some of these disturbances may also be encountered in frontal lobe lesions,[28] we look in vain for these ups and downs in analyzing the dysfunction of the posterior associational fields. With the apparent exception of overproduction of speech impulses in some cases of sensory aphasia they are invariably minus functions, due either to local lesions or to disorders of impulse transmission from the anterior association areas. It is relatively insignificant whether these disturbances are due to absence or disease processes of the frontal lobes, as both conditions deprive the posterior association fields of normal impulse reception.

In spite of the close integration of the anterior and the posterior associational fields their contribution to the total psychic process is a different one, depending, in the last analysis, on their connections with subcortical centers, their histologic features and their phylogenesis. Disease processes implicating different parts of this mechanism involve different factors which, under normal circumstances, add their quotas of action to the total process. Thus, involvement of the anterior association fields by bilaterally spreading tumors of the genu of the corpus callosum on the one hand, and of neoplasms of the splenium on the other, will give rise to syndromes that include similar elements, although in significantly different proportions.

Speaking in more detail, the mechanism of mental disturbances in tumors of the corpus callosum appears to be the following:

(a) *Bilateral tumors of the genu of the corpus callosum* (bilateral frontal lobe tumors) deprive the total process of the complex frontal factors. Emotional disturbances and derangement of other homeostatic mechanisms, important chiefly for the maintenance of awareness and concentration, are prominent features.

(b) *Bilateral tumors of the splenium of the corpus callosum* (bilateral temporo-parieto-occipital tumors in advanced cases) deprive the total process of the mnestic associative factors, the clinical syndrome being characterized by conspicuous disturbances of memory and higher mental functions that depend on the utilization of engrams. It is suggested that difficulties in concentration in these cases are essentially repercussions of the inadequacy of local engram formation and their faulty utilization, which may deepen into severe confusion resembling or actually approaching disturbances in consciousness.

(c) *Bilateral tumors of the midportion* of the corpus callosum are essentially neoplasms of the cingular gyri overlying the neoplastic focus in the callosal body. It has already been mentioned that the cingular gyrus contains a long association tract, connecting the frontal with the temporo-parieto-occipital lobe.* While the long cingular fibers appear to be of significance for the correlation of the highest levels of psychic activity, the effects of lesions of the fasciculus cinguli in different localities are probably not uniformly severe. The relatively rare and less severe mental changes observed in tumors of the midcallosal region may be taken as suggestive evidence that pathological processes involving its anterior segment implicate also intrafrontal; of its posterior segment, intraparieto-occipital fiber systems in addition, of course, to local cortical fields.

Freeman and Watts[14] observed that their patients lost contact with reality and developed disorientation and confusion at the very moment in which a small bundle of fibers running above the rostrum of the corpus callosum was cut, which, they believe, was the fasciculus cinguli. Scoville,[43] severing the white matter of the frontal lobe alongside this fiber bundle, significantly failed to produce any changes.

(d) *Unilateral frontal lobe tumors*, such as convexity meningiomas may be clinically silent for a long time as far as mental changes are concerned, while gliomas which spread into the opposite frontal lobe through the genu of the corpus callosum produce mental changes which are almost

*The fasciculus cinguli is more prominent in macrosmatic animals, and originally represents a link between the frontal and the temporal olfactory centers. With rise in the phylogenetic scale a neocortical contingent of fibers is added (Redlich[36]).

as frequent and severe as those in bilateral neoplasms. Propagation of dysfunction through the entire cross section of the rostral part of the corpus callosum appears to be the most likely explanation.

(e) Similar conditions should prevail in *unilateral tumors of the posterior portion of the corpus callosum* as mental changes in the three (predominantly right sided) gliomas of our series were essentially identical with those in the nearly symmetrical bilateral tumors. In speaking of unilateral tumors it should be kept in mind that the cingular gyri are implicated on either side in nearly every case.

(f) *Unilateral tumors of the midportion of the corpus callosum* sooner or later involve the fasciculus cinguli of the opposite hemisphere by pressure, if not by infiltration.

2. *Frontal lobe signs* were encountered less frequently. Hyposmia on the side opposite the major portion of the lesion was noted in case XII. One patient (case VI) was unable to identify odors by name. There was a bilateral positive grasp reflex in cases XIX and XX.

The mechanism of hyposmia in case XII is not clear. Economo and Koskinas[12] placed the primary olfactory center in the retrosplenial region (area 29). If these centers were actually located there one might assume hyposmia to be a more frequent abnormality.

The author[40] observed and partly removed a solitary metastasis encroaching upon the left side of the splenium which had produced uncinate attacks. Olfactory hallucinations were also present in cases II and XIV. These observations suggest that the retrosplenial region is an olfactory center of a higher order rather than one analogous to the primary neocortical centers.

Since the positive grasp reflex in the two cases XIX and XX was in all likelihood due to clouding of consciousness and case VI, too, showed considerable mental deterioration, there remains only one case (XII) in which a frontal lobe sign was present.

3. *Basal ganglia signs* were noted in seven cases (35 per cent). A parkinsonian-like tremor in the right upper extremity was present in cases II and X, retropulsion in case II, slight general rigidity in case II, a continuous coarse tremor in both trunk and the proximal parts of both lower limbs in case IV, akinesia in case XVIII, attacks of rhythmic opening and closing of the jaw in case XIII, and a generalized tremor, more marked on the left side, in case XVII. A "peculiar transitory paralysis of voluntary movements in one arm or the other" in case V may be listed tentatively as sign of involvement of the basal ganglia.

The only relevant evidence that could be gathered from the autopsy records was unilateral destruction of the head of the caudate nucleus in

case XIV. Otherwise, the autopsy findings threw no light on the clinical abnormalities. Whether tumefaction of the corpus callosum either compressed the basal ganglia or gave rise to local edema cannot be definitely stated.

4. *Thalamic signs* were absent. A careful perusal of the various reports suggests that there were no thalamic signs proper, although involvement of the thalamus is noted in cases VI, X and XVII.

5. *Hypothalamic signs* were present in six cases (30 per cent). Increased desire to sleep was observed in cases I, IV, III and XVIII, sleeplessness in case VI, persistent elevation in temperature for which no other reason could be found in case XIII, and emaciation in case VI.

Ironside and Guttmacher[21] believe that the drowsiness observed in case III was due to encroachment of the third ventricle by the lesion, and the same explanation may hold true for the derangement of a homeostatic mechanism in other spheres of automatic functions. (The cerebrospinal fluid in case XIII contained no blood.)

6. *Sensory-motor signs* were noted in 17 cases (85 per cent).

Considering the interdigitation of callosal fibers with those of the internal capsule and the spread of the neoplasm along the fiber bundles of the corpus callosum, the high incidence of sensory and motor findings is not surprising. The backward sweep of the sensory and motor fibers into the subcortex of the parietal lobe[34] may be an additional reason for the high incidence of sensory-motor signs. While bilateral pyramidal tract signs were present in seven cases, extensive bilateral involvement of the hemispheres was noted in four cases only (II, XIII, XVIII and XIX).

7. *Temporo-parieto-occipital signs* were present in 10 cases (50 per cent).

Olfactory hallucinations were reported in cases II and XIV, formed visual hallucinations in case VI, left sided visual attention hemianospia in cases I and II.

Sensory aphasia and agraphia were present in cases IV and XIX, inability to operate with figures in cases X, XIX and XX, inability to read figures and to write mathematical symbols in case XX, inability to gauge distances in case VI, visual agnosia in cases VI, XIX and XX, left-right disorientation in case XIX, apractic difficulties in performing with fingers and minic musculature in case XX, apraxia (not specified) in case XI, and ideokinetic apraxia in cases X, XVIII and XIX.

Considering the type of spread of the lesion along the forceps posterior it is surprising that hemianopic field defects suggestive of unilateral or partial bilateral involvement of the optic radiation were not mentioned more frequently. Lack of cooperation on the part of the patients (which

was mentioned in one or two cases) may have been responsible for the relative lack of positive findings on perimetry.

It appears worthy of mention that apraxia was noted in five cases only (x, xi, xvii, xix and xx).

8. *Brain stem signs* were frequent. Ocular disturbances referable to the midbrain were observed in nine cases (45 per cent). In two cases (v and xx) paroxysmal atonia in the lower extremities was noted.

Bilateral irregularity of the pupils was present in cases iii and x, bilateral sluggishness of light reaction in cases iii, bilateral mydriasis in case vii, bilateral absence of light reaction in case x, unilateral absence of accommodation reaction in cases xii, xiii and xviii. In case xi, absence of light reaction and sluggishness of light reaction were found on opposite sides. Alternating variations in the size of the pupils were present in case xiii, unilateral mydriasis, absence of light reaction and intermittent ptosis in case xx, impairment of upward gaze and pupillary disturbances (not specified) in case v. In case xx, unilateral abnormalities were followed by bilateral disturbances.

Suggestive evidence of involvement of the ocular midbrain mechanism were: (a) the presence of several abnormalities compatible with midbrain involvement, occurring either simultaneously or in succession, (b) the absence of concomitant unilateral external ocular and other cranial nerve palsies, (c) the presence of other signs of midbrain involvement, and (d) postmortem findings. In one only case (v, Hyslop[20]), was it noted that "the corpus callosum in its posterior aspect was pressed downward and forward against the upper portion of the midbrain and pons." In case xiii, (Mahoudeau[27]), the pupillary disturbances were explained by the author as being due to midbrain compression. While the remaining autopsy protocols do not suggest that the disturbances in question were definitely caused by compression of the midbrain it should be emphasized that patency of the iter or absence of flattening of the quadrigeminal plate in brains that have not been hardened prior to their removal do not exclude the possibility of midbrain compression during life. The possibility of a bilateral cingular herniation in the retrosplenial and subsplenial region across the margin of the tentorium, with resulting compression of the superior colliculi and of venous congestion within the midbrain, should also be taken into account.

Paroxysmal atonia in the lower extremities* occurs in both midbrain

*Sudden loss of muscle tone, not accompanied by unconsciousness and involving apparently all muscles rather than those of the lower extremities only, is sometimes referred to as cataplexy (Wilson[50]) or akinetic epilepsy (Lennox[25]). The condition should not be confused with syncopal attacks which also occur quite frequently in frontal lobe lesions.

and frontal lobe lesions.[19] While gross disturbances in standing and walking due to extreme hypotonia rather than ataxia may occur in lesions of the midbrain, the type of disturbance in station and gait in cases VII, XII, XVII and VI, for example, appear to indicate the involvement of a cerebellar rather than a midbrain mechanism. It is quite possible, therefore, that tumors of the splenium may involve not only fronto-mesencephalic but also cerebello-rubral connections.

9. *Cranial nerve signs* were noted in case II only, in which one pupil was larger than the other. The relative absence of cranial nerve signs in tumors of the corpus callosum has been described by various authors.

10. *Cerebellar signs* were observed in nine cases (45 per cent).

Intention tremor was present in case II, unsteady, widebased gait in cases VII, XVIII, XI and XII, spontaneous nystagmus in cases X, XVII and XVIII, vertigo in cases VII, X and XVII, lateropulsion in cases XVIII, XII and XI, abasia in cases VII and XVII, areflexia in cases X, XIII and XVIII, tremulous speech in cases XIII, and hemiataxia in cases XI.

Compression of the cerebellum by the lesion was noted in the autopsy findings of case XVII only.* Whether the neighborhood effects of the neoplasm might have involved the decussation of the superior cerebellar peduncles or the red nuclei is conjectural, but it appears to be worthy of note that cerebellar and midbrain signs were frequently associated (cases VII, X, XI, XII, XIII, XX). In three cases only (III, V, XX) there were midbrain signs without cerebellar signs, and an equal number of cases (II, VI and XVII) showed cerebellar without midbrain abnormalities. Hemihypesthesia was a complicating feature in only three out of the nine cases in which cerebellar disturbances were found (III, XII and XVIII) and probably was of no significance. It does not appear from the description of the locomotor ataxia in any of the cases that "callosal ataxia" (Zingerle[51]) might have been an apraxia of gait.

(11) *Signs of intracranial hypertension* were present in 14 cases (70 per cent); papilledema in 13 (65 per cent). A definitely elevated cerebrospinal fluid pressure was noted in cases XIX and XVII only. Generalized headaches and vomiting occurred in several cases.

12. *Physical and systemic signs suggestive of an intracranial pathological process*, such as dilated veins of the scalp, unilateral exophthalmos, were absent.

13. *Laboratory findings* are often of importance. Abnormalities of various cerebrospinal fluid constituents were noted in nine cases, or 45

*The rostral part of the superior vermis and the adjacent portions of the quadrangular lobe of the cerebellum, which are not protected by the tentorium present upward, facing the lower surface of the splenium of the corpus callosum.

per cent (I, II, V, VII, X, XIII, XVII and XIX), the most frequent findings having been xanthochromia and pleocytosis. Pleocytosis was present in eight cases, in four of which the cells were lymphocytes. The cell count ranged between 16 and 322 cells, the average being 96. The total protein was elevated in four cases, and the colloidal gold reaction was positive in two. Xanthochromia was found in four cases.

While it is known that xanthochromia may occur in callosal tumors, this finding is usually not given sufficient attention. The discoloration of the cerebrospinal fluid is probably due to seepage from the vessels of the glioma into the cerebrospinal fluid spaces. The lesion was bilateral in seven out of the nine cases in which spinal taps were reported to have been performed. It is hardly necessary to point out that mental changes observed in this series cannot be generally attributed to the presence of blood in the cerebrospinal fluid. A sudden exacerbation of the mental disturbances in case XVI,[26] which occurred shortly before death and which consisted of sudden agitation and confusion, may have been due to an episode of rather severe bleeding from the tumor, for which there was evidence at autopsy. In this case, the sudden intensification of the mental disturbances was accompanied by a rise in temperature.

14. *Non classifiable neurologic disturbances* were of various types. One case showed "clonic twitchings brought out by voluntary movements" which are difficult to explain. It cannot be stated with certainty whether a "peculiar paralysis of voluntary movements in one extremity or the other" can actually be accounted for by involvement of the basal ganglia or represents what Akelaitis[1] termed "diagnostic dyspraxia." There was difficulty in micturition in case XII.

15. *Miscellaneous* data should be mentioned. The sex of the patient was noted in 18 of the 20 cases. Eleven were males and seven females.

The age was given in all cases. Eighteen cases were over 40 years old, three having been over 70 at the time of the onset of the disease. Most cases occurred in the age group between 45 and 62 years. The average age was 53½ years.

The duration of symptoms between the onset of disease and hospitalization of the patients was noted in 13 cases only. Case VIII, an oligodendroglioma, had a 12 year history; case VI, a fibrillary astrocytoma, an eight year history. There was a history of three weeks duration in case VII. The duration of the illness prior to admission was approximately two years in case XI, one year in cases II, III, XVI, XVII, XIX and XVIII, six months in case X, and two months in cases I and XV.

The disease started with mental changes in ten cases (50 per cent)

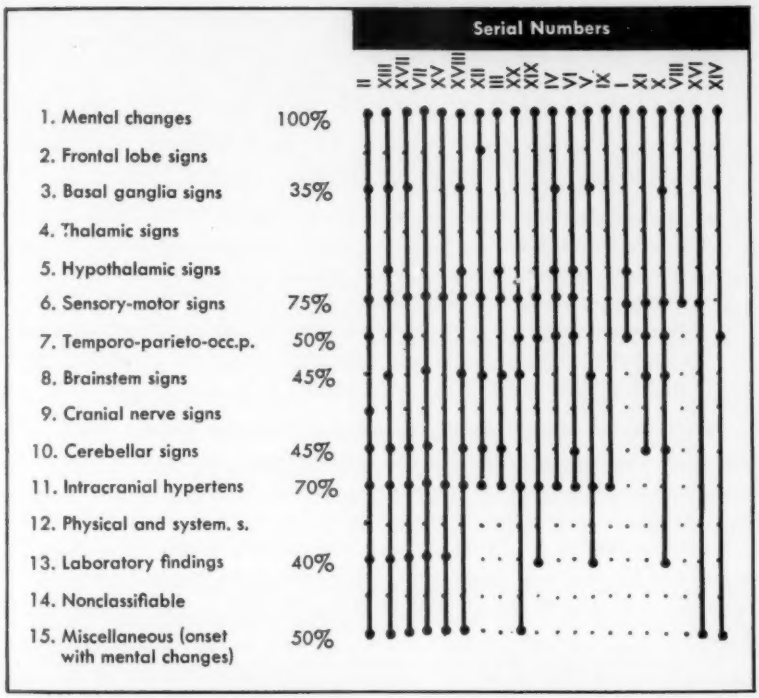

FIG. 2. Neurologic abnormalities and laboratory findings in gliomas of the splenium of the corpus callosum. Large dots indicate presence and small dots, absence of the various manifestations in the individual cases (represented by vertical lines).

(cases II, III, VII, XIII, XIV, XVII, XVIII and XX). In the remaining eight in which the type of onset was reported, mental changes either appeared almost simultaneously with or very soon after the inaugural manifestations. The disease started with sensory-motor signs in cases I and VIII, with hypothalamic signs in case V, signs of intracranial hypertension in case X, and with cerebellar signs in cases XI and XII.

It would appear that gliomas of the splenium tend to occur at a somewhat higher age than the average glioma of the cerebral hemisphere. Both the frequent onset with mental changes and the rare onset with signs of increased intracranial pressure are of practical importance. Otherwise, the course of the disease is in no way suggestive of any particular location. Neither can any special significance be attributed to the various "averages," computation of which appears to be required by tradition.

DISCUSSION

Most of the clinical facts noted in the present series of gliomas have already been commented upon. Other points which are of practical and theoretical interest still need some clarification. The incidence of various groups of disturbances is shown below. The most frequent abnormalities (occurring in more than one-third of the total) were:

Mental changes	(100%)
Sensory-motor signs	(85%)
Intracranial hypertension	(70%)
Temporo-parieto-occipital signs	(50%)
Brain stem signs	(45%)
Cerebellar signs	(45%)
Basal ganglia signs	(35%)

It would be entirely wrong to assume that the lesions under consideration are characterized by the simultaneous presence of the most frequent signs. It should be emphasized, therefore, that a combination of the disturbances tabulated above did not appear in a single case of the entire series (figure 2). Whether such a syndrome might have been observed had the series of cases been larger and, if so, would be pathognomonic for a glioma in the location under discussion, cannot be answered at present.

A consideration of the eight cases showing pleocytosis of the cerebrospinal fluid (XIII, II, XVII, VII, XIX, V, I, XV) shows a tendency to a combination with several (from three to six) of the most frequent clinical manifestations of the lesion and, of course, a regular association with mental deterioration. Even so, the syndrome lacks at least one of the most frequent clinical findings.

Provided that the inclusion in the records of negative cerebrospinal fluid findings has not been neglected, the presence of pleocytosis (with or without other cerebrospinal fluid abnormalities) gains added importance in that they were present in eight out of nine cases in which a spinal tap was performed.

While the general trend of the disease to produce certain abnormalities is unmistakable, a combination of the whole series of "characteristic" clinical and laboratory findings must be very rare indeed. However, if a middle aged person or one past middle age develops mental changes, chiefly profound disturbances in memory and the abnormalities in behaviour resulting therefrom, cerebrospinal fluid pleocytosis, (with or without xanthochromia and other abnormalities), signs of intracranial hyper-

tension, and a series of pathological findings pointing toward midbrain, basal ganglia and cerebellum, in other words a "disseminated" localization, a glioma of the splenium of the corpus callosum should be considered the most likely clinical diagnosis. Cases II, VII, XIII and XVI answer this description most closely.

It might appear from the present series that less than one case out of twenty can be diagnosed on clinical grounds, but since the incidence of cerebrospinal fluid changes should be considerably higher than 40 per cent, a tentative diagnosis may perhaps more frequently be made. In many cases, however, the disease may be masquerading as senile or presenile psychosis, Korsakoff's psychosis, or general paresis until its neoplastic nature is recognized by the clinical course and the cerebrospinal fluid findings.

SUMMARY

1. Gliomas of the splenium of the corpus callosum develop mostly in persons past middle age, and frequently produce profound disturbances in memory in the inaugural phases of the disease, prior to the onset of intracranial hypertension.

2. Mental changes were present in 100 per cent, sensory-motor signs in 85 per cent, intracranial hypertension in 70 per cent, temporo-parieto-occipital signs in 50 per cent, brain stem signs in 45 per cent, cerebellar signs in 45 per cent, and basal ganglia signs in 35 per cent of the cases. The frequent occurrence of cerebellar and midbrain signs, which were apt to be associated, is probably due to both direct and indirect pressure effects in the region of the tentorial notch.

3. The gliomas under consideration, most of which belong to the spongioblastoma multiforme group, are apt to produce seepage of blood into the subarachnoid fluid spaces and irritation of the meninges with resulting xanthochromia, pleocytosis and increase in total protein. Cerebrospinal fluid abnormalities were present in the nine cases in which a spinal puncture was performed.

4. Due to the absence of neurologic abnormalities in the early and the distant effects of the neoplasm in the advanced stages of the disease, their clinical diagnosis is difficult. The cerebrospinal fluid findings, therefore, gain added importance.

5. An attempt has been made to account for the presence and different types of mental changes in tumors of the splenium, the midportion and the genu of the corpus callosum.

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Structure of nerves.—The nervous system consists essentially of receptive or controlling ganglionic centres, and of the nerves which connect these with one another and with the skin, muscles, and viscera. Nerves are usually divided into those known as cerebro-spinal and those belonging to the great sympathetic system. The former chiefly concern us at present, since, indeed, the latter are rarely injured, and since their diseases have only of late begun to claim attention. The former, often known as nerves of animal life, are such as emerge from the encephalon or from the spinal axis, and carry to every part of the body excitations originating in the great centres, or in turn bring to these the numberless impressions arising from without, or having birth within the tissues themselves Yet, varied as seems to be the character of the messages with which they are charged, an astonishing sameness of structure marks the organization of all these fibres.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Failures in Migraine Therapy

Arnold P. Friedman, M.D.
and Theodore J. C. von Storch, M.D.

THERE have been numerous reports concerning successful treatment of migraine. However, there are many failures in any large series of unselected cases. An analysis has been made of failures occurring in a series of 600 unselected cases, but no attempt has been made to present statistical evidence. This report is concerned primarily with trends and impressions which have been the natural consequence of a thoughtful and careful consideration of therapeutic failures and successes during the past ten years. These impressions are presented as a stimulus to further positive investigation.

It would appear that the most common causes of therapeutic failure are: incorrect diagnosis; inappropriate, inadequate or improper administration of medication; inflexibility of therapeutic regime; failure to recognize the variable etiology of the syndrome; additional factors associated with the attack; and finally the vital role of the patient-physician relationship.

Incorrect diagnosis is, of course, the primary hazard. There are quite a few disorders that on occasion may closely simulate the rather protean manifestations of the migraine syndrome. The more important of these disorders are listed in table 1. As is true in any medical problem, a careful history, examination and certain ancillary tests are necessary in differential diagnosis, but a detailed history including personality evaluation is of utmost importance in diagnosis of migraine. Laboratory procedures are least valuable.

Inappropriate symptomatic therapy is a cause of certain failures. Approximately 85 per cent of the cases under study responded satisfactorily to vasoconstrictors, particularly the ergot derivatives (figure 1).[1] Of the

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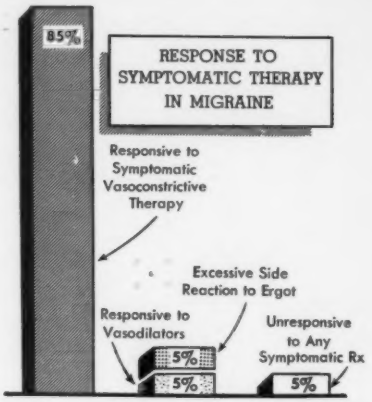

remaining 15 per cent, about 5 per cent either could not tolerate the ergot compounds because of excessive reactions such as nausea, vomiting and periarterial pain, or were unable to use them because of contraindications such as coronary or hepatic disease, hypertension, etc. Another 5 per cent responded better to the vasodilators. Contrary to certain opinions,[2] it was not possible to define this group without therapeutic trial. A final 5 per cent were refractive to anything except strong analgesics or powerful sedatives. In certain of these cases a combination of several symptomatic therapies was effective.

Another cause of therapeutic failure is *inadequate or improper use of medication*.[3] In the case of ergotamine tartrate and other ergot derivatives and compounds, there are several common errors. Treatment is often started too late in the attack. Usually more medication is necessary when administered after an episode is well developed. Failure is often due to an inadequate initial dose. There is no place for timid treatment in true migraine. The route of administration is another factor determining success or failure. Oral administration of ergot and caffeine was effective in about 85 per cent of the cases reported here. In a few instances, parenteral administration is necessary because of vomiting associated with the attack itself. However, rectal suppositories have been found as effective as hypodermic injections, sometimes more effective, and always more convenient. Nausea and vomiting are minimal with rectal medication.

Another cause of failure in the symptomatic treatment of migraine is *inflexibility*. Each episode varies somewhat in severity according to the impact of current endogenous and exogenous environmental contacts, i.e. the "life situation." Hence the treatment schedule must vary in dosage and even route of therapy according to the situation at hand. Many episodes may be fairly similar in type and degree while others are accentuated or otherwise altered by concomitant emotional stress.

Failure to recognize additional factors associated with the attack may result in much disappointment. As has been ably demonstrated by Wolff, et al.,[4] the addition of muscular spasm in neck and scalp may cause persistent cranial pain after the vascular element has subsided. This complication requires thermal applications, postural alterations or non-specific

TABLE 1

VARIOUS CONDITIONS CAUSING HEADACHE WHICH MAY BE CONFUSED WITH MIGRAINE

TUMORS

Neoplasms —Especially lateral ventricle and ball valve tumors
Aneurysms —Usually cause persistent ocular signs
Hematoma —Especially subdural in older people

TRAUMA

Post traumatic encephalopathy—with objective evidence
Post traumatic psychogenic headache
Scalp scars and other injury

INFLAMMATION

Sinusitis —Frontal, ethmoidal, sphenoidal
Sluder's vacuum type
Temporal arteritis

ENDOCRINE

Gonadal —Menstrual
Menopausal
Hypothyroid

SYSTEMIC

Arterial hypertension
Anemia

SPECIFIC

Ocular —Glaucoma
Astigmatism
Convergence insufficiency
Cervical —Myalgia, arthritis, discs, dislocations and tumors
Histamine —Horton's histamine headache

NEURALGIAS

Craniofacial —Occipital—temporal—trigeminal
Ciliary—sphenopalatime—glossopharyngeal
Atypical facial migraines

TENSIONAL

Cervical —Muscle tension due to inflammation trauma, etc.
Scalp —Muscle tension due to inflammation trauma, etc.

EMOTIONAL

Physiologic —Tensional (muscle) } caused by pain and/or anxiety
Vascular (dilation) }
Psychogenic —Conversion
Symbolic

analgesics. Persistent vasodilation may cause structural changes in the cranial blood vessels rendering them irresponsive to vasoconstrictor therapy.[5] Here again analgesics may be necessary.

Occasionally other *unrelated complications* must be considered such as debility, fatigue or infections. Unless these are dealt with specifically, symptomatic therapy is often negated.

In the authors' experience the *patient-physician relationship* is one, if

not the most important, factor in both symptomatic and prophylactic therapy. In some instances, confidence transferred to patients by overly enthusiastic therapists may account for many of the good but temporary results of various methods—and for the fact that they cannot be duplicated by more critical observers. This confidence in physician, regime or medication, though of great practical value, must always be considered in evaluating any therapy. It is vital to the therapist, therefore, to be keenly aware of this relationship at all times if he is to understand, forecast and skillfully direct the course of treatment.

Unfortunately prophylactic therapy is much less effective than symptomatic therapy. It is quite possible that the basic etiologic factors upon which prophylactic therapy is founded vary considerably from one case to another. Thus the therapeutic approach must be adapted to the situation at hand. Prophylactic therapy must be based upon an unbiased analysis of each individual and not upon the therapist's particular point of view. Thus certain cases will respond at a cortical, others at an autonomic or humeral level. No single prophylactic measure has yet been universally effective. Most of the recommended medical procedures involving allergy, the endocrines, etc. have not been successful in the authors' experience. It is indeed a very curious disorder in which the allergist cures 50 to 80 per cent, the ophthalmologist 90 per cent and the endocrinologist is equally successful. Again, it is reported that cervical traction relieves 85 per cent, histamine infusion 75 per cent and psychoanalysis 100 per cent. What factor is common to these diverse methods is still a matter for speculation.

At present the most promising therapy appears to be psychoanalytically oriented psychotherapy of an informal nature including doctor-patient relationship, ventilation and verbalization, and environmental adjustment. Catharsis, desensitization, redirection and re-education are important parts of such therapy. Thus the patient becomes aware of previously unrecognized drives. Every effort is made to modify underlying tension and also to alter the environment, thus establishing a more secure and stable pattern of life. This type of psychotherapy, plus symptomatic treatment, has reduced the frequency and severity of headache in about 65 per cent of our cases.[1]

Even if one adheres closely to the principles just outlined, there remain about 15 per cent of patients who are refractory to symptomatic treatment and at least 35 per cent who are refractory to all preventive methods. From an analysis of group of 600 cases, it appears that the most significant factors in the refractory patients are as follows (figure 2):

A. The family history in these cases reveals a preponderance of migraine in a ratio of 90 per cent in the refractory to 60 per cent in the non-

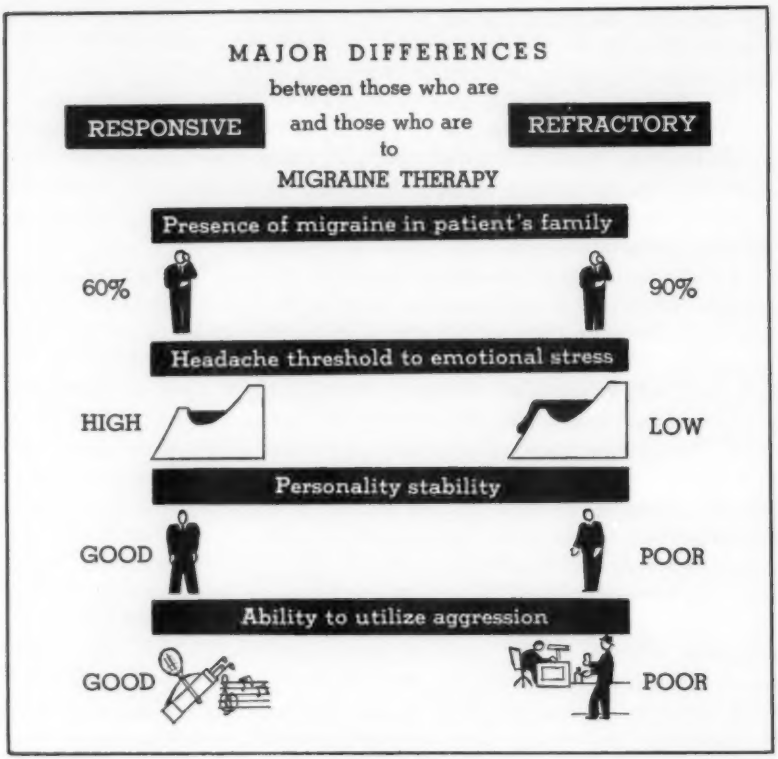

FIGURE 2

refractory group. Whether this reflects a genetic or environmental factor is still open to question.

B. These patients apparently have a much lower headache threshold as represented by an intolerance to emotional trauma. It requires much less stress to precipitate an attack. This may represent an unstable autonomic reaction to emotional stimuli.

C. The personality disturbance seems greater in degree although no specific personality type is manifest. In the refractory cases there appear to be more neurotic traits in childhood. As adults there is great rigidity, considerable aggression, and an inadequate sexual adjustment. However the truly significant difference between the two groups is that in the refractory cases there is a pronounced deficiency in the mechanisms whereby patients utilize their aggression.

SUMMARY

A review of the therapeutic failures occurring in an unselected group of 600 patients with migraine has revealed and crystallized certain impressions.

These observations indicate that (1) symptomatic therapy in migraine must be flexible and individual; (2) variable, accessory and complicating factors must be considered in each case; (3) more intensive psychotherapy is indicated in both refractory and responsive cases.

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The most interesting generalizations as to trophic changes consequent upon lesions of nerve trunks are these:

Total section of the main nerves of a limb results invariably in atrophy but not necessarily in any inflammatory conditions. It does not, however, forbid these, nor is repair always interfered with to any great extent.

Partial wounds of nerves, and especially gunshot lesions, are apt to give rise to a large number of trophic changes in the skin, hair, nails, areolar tissue, and muscles. Except the entire arrest, for a time, of nail growth, every trophic alteration capable of arising from injuries or diseases of the centres is also to be met with as a consequence of wounds of the nerves.

Section of muscle nerves causes atrophy and contraction of the related muscles. Partial wounds occasion various degrees of wasting, with more or less loss of muscular sensation, and impairment or loss of power to respond to electric, galvanic, or mechanical irritation.

Trophic changes are most prone to follow wounds of nerves which are distributed to the hands and feet, and more rarely occur when the injury has involved only the nerve branches which supply the upper portions of a limb.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Neuropharmacologic Considerations in Psychic Seizures

James E. P. Toman, Ph.D.

Until twelve years ago the clinical control of convulsive disorders was relatively poor, with phenobarbital[24] and bromide[42] as the most useful agents available. The introduction of diphenylhydantoin by Merritt and Putnam in 1938[50] opened a new era in the therapy of major seizures, but left the various categories of partial seizures relatively untouched. More recent extensive studies on the mechanism of spread of seizure activity suggest that diphenylhydantoin suppresses this mechanism, thus preventing major seizures without necessarily abolishing discharge of the primary focus.[71, 73]

The petit mal triad was the second group of convulsive disorders to be brought under therapeutic control with the introduction of trimethadione by Richards and Perlstein in 1945,[60] its validation by Lennox[35] and others,[23, 55] and the subsequent success of the closely related Paradione.[9] In spite of many experimental studies, little is known of the mechanism by which the oxazolidine-2, 4-diones suppress the discharges characteristic of petit mal, other than that they appear to elevate the threshold of the discharging focus. Recent evidence[25, 28] makes it increasingly probable that the petit mal focus is a subcortical center with extensive bilateral connections to the cerebral cortex. This factor, together with the high CO_2 sensitivity and hypersynchronization characteristic of petit mal, should be taken into account in connection with the high degree of specificity of trimethadione and Paradione.

The most refractory group of seizures remaining are those partial seizures, including the psychomotor, having a cortical focus of origin and manifested by slowly repeated sharp wave patterns in the electroencephalogram. Their bizarre clinical variations and their resistance to therapy have placed them among the most challenging diagnostic and therapeutic problems in neuropsychiatry. The introduction of Mesantoin

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by Kozol in 1946[30] and Phenurone by Gibbs et al. in 1948[19] offers promise for their clinical control, but much remains to be learned about the peculiarities of this type of seizure, as well as the specificity of the few drugs effective at present.

Some observations on partial seizures of cortical origin in man and animals will be presented which may cast some light on the mechanism of psychomotor seizures, and the pharmacology of drugs which have been used with more or less success in their control will be discussed.

CHARACTERISTICS OF PSYCHOMOTOR AND RELATED SEIZURES

Clinical

Hughlings Jackson[26] recognized a group of partial seizures having psychic aspects, including "dreamy states" with evidence of basal temporal lobe involvement. His interpretation of these seizure variations was anatomic and dependent upon both the focus of excessive discharge and the areas of brain in which function was disrupted by spread of the excessive focal activity.

With the advent of electroencephalography, there was postulated a typical psychomotor pattern consisting of diffuse "square" or "sawtooth" waves (actually slowly repeated sharp waves).[20] Unfortunately it was not clearly recognized at that time that the generalization of the pattern arose from the use of a common ear lead in monopolar recording. More recently Gibbs[17] has observed a predominantly temporal or pretemporal focus of negative sharp waves in psychomotor cases.

Meanwhile Penfield and his colleagues[53, 54] have pursued Jackson's original thesis that the clinical type of seizure depends upon the initial site of the discharges, which may or may not spread to give a final common type of major seizure. Among psychic seizures these investigators include hallucinatory attacks of temporal lobe origin, paroxysms of stereotyped behavior or automatism arising with prefrontal lesions, and episodes of "forced thinking" associated with lesions in the posterior frontal lobe, as well as various postictal states of confusion and automatism. Apparently there may be several possible sites of origin of discharges resulting in partial seizures with aberrations of perception, behavior or affect.

Since the brain is normally capable of manifesting major seizures, the question arises as to why all partial seizures do not spread completely to give convulsions. Antoni[2] has offered the suggestion that temporal lobe discharges have a relatively long path of spread and easily "get lost" on the way, with the result that only the aura or a dreamy state seizure may occur. He points out the frequency with which major seizures may be reduced to psychic seizures by anticonvulsant medication.

However, there is another feature of partial seizures which should be taken into account in a discussion of their failure to spread. The frequency of discharge of many types of cortical lesions is characteristically slow, as in the so-called petit mal variant electroencephalogram and the temporal sharp wave pattern of many psychic seizures. But the mechanism of spread of seizure activity seems to require a propagation of high frequency neuronal discharges.[1] Is it conceivable that a slow rate of discharge from a focus militates against actual spread of seizure activity but still succeeds in disrupting the normal activity of the cerebral cortex as a whole by repeated hyper-synchronizing bursts of impulses? The ability of low frequency stimulation to produce partial seizures in animals (see below) strongly suggests such a possibility.

Partial seizures resembling psychomotor attacks are often seen in human electroshock therapy when voltages close to threshold are used. The patient may appear merely stunned, show automatisms of psychomotor type, or develop a masticatory type of attack. These partial seizures sometimes progress after a long latency into a major convulsion, or may be converted into a tonic-clonic seizure by a second shock without increased voltage.[74] The incidence of bizarre partial attacks is much increased by pretreatment with anticonvulsant medication, even when voltages well above threshold are used, making possible a human assay method for anticonvulsant drugs.

Experimental

The character of seizures produced in experimental animals by electrical stimulation of the brain depends in part upon the parameters of stimulation. With the conventional stimulus frequency of 60 cycles or above (for sinusoidal waves or rectangular pulses) and voltage and duration 25 per cent or more above the threshold for a minimal seizure, the typical seizure pattern in laboratory animals is a stereotyped and maximal tonic-clonic convulsion. The character of the attack is easily altered by anticonvulsant drugs to the point where no intensity of stimulation will produce the typical tonic-clonic sequence. Particularly with diphenylhydantoin the convulsion may be reduced to a prolonged and bizarre but coordinated running type of attack. Electroencephalographic records during such seizures show grouped spikes or sharp waves instead of the high frequency spikes characterizing a full tonic seizure. The drugs most effective clinically against major seizures show the greatest margin of safety between seizure-modifying and behavior-modifying dosage levels. This correlation has been made the basis of a simple assay method for anticonvulsants.[75]

With a lower frequency of stimulation, it becomes increasingly more

difficult to produce seizures having a tonic phase.[72] For example, with 9 msec rectangular pulses at 5 per second delivered through corneal electrodes, the threshold for clonic seizures in rats is found to be approximately 25 mA, while 250 mA are required to elicit a tonic element. Throughout the intervening range of stimulus strength, the seizures produced by low frequency stimulation are mild and clonic, lasting an average of 28.5 seconds. There is little evidence of neurologic depression during the clonic seizure. It is usually limited to the face and forefeet, the latter alternating in a slow and seemingly purposeful automatism, while the animal maintains a quadrupedal or more typically a bipedal standing posture. Following the overt clonic attack, the rats show evidence of continuing abnormal behavior for a period averaging 69 seconds but ranging from 12 to 115 seconds. They stand quietly without making the normal exploratory movements, and can be moulded into various standing postures. Abruptly following this catatonic phase, normal walking and exploration begin. Infrequently the abnormal behavior can be induced without a preceding clonus by threshold stimulation alone.

This type of seizure has been found remarkably resistant in pattern to the usual anticonvulsants. The pattern is not significantly altered by doses of anticonvulsants sufficient to change the pattern of tonic-clonic seizures induced by high frequency stimulation, but the threshold for production of the low frequency seizure may be increased.

Because of the clonic element and the superficial resemblance to a petit mal absence, it might be thought that attacks induced by low frequency stimulation belong properly in the petit mal group. However, the relatively long duration of the total attack and the asymmetrical and deliberate character of the clonus are also reminiscent of psychomotor attacks. Therefore electroencephalographic studies have been undertaken to aid in the differentiation. Rabbits, which show similar overt seizures, are used for convenience, and stimulation and recording are performed through insulated epidural electrodes. Even below the threshold for minimal overt motor clonic seizures, it is found that slow afterdischarge can be produced in the electroencephalogram. The afterdischarge bears no resemblance to the typical symmetrical spike and wave pattern of petit mal. It usually consists of slow and somewhat irregular sharp waves, frequently giving the appearance of the so-called "sawtooth" or "square-topped" pattern once thought to be pathognomic of psychomotor epilepsy. The discharges are frequently asymmetric. A typical example is shown in figure 1. Although the threshold for production of these discharges can be raised by a number of agents including Phenurone, the pattern of the seizure, once achieved, is not notably altered by drug action.

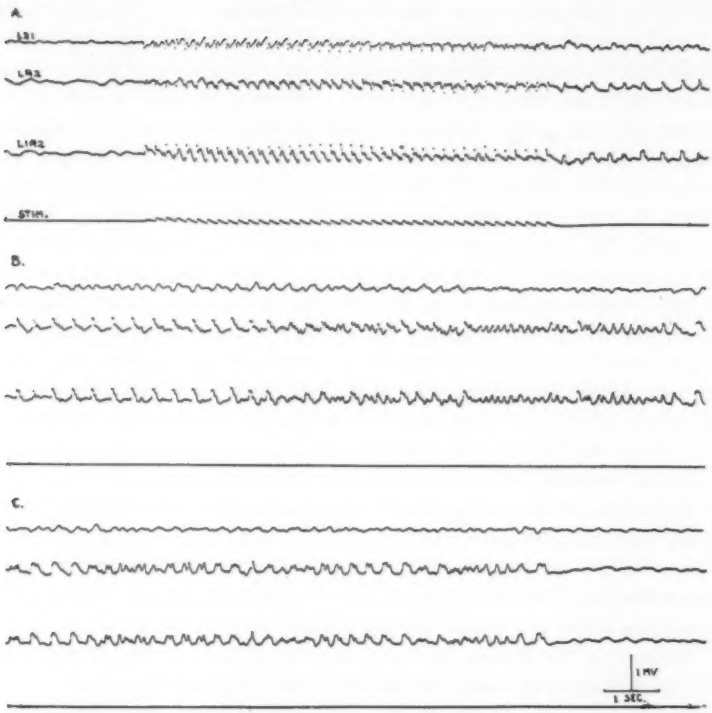

FIG. 1. Partial seizure following low frequency stimulation of the cerebral cortex of the rabbit.

Stimulation at approximately 2x threshold voltage with pulses of 0.9 msec. duration and 5/sec. frequency for 8 sec. through implanted epidural electrodes; cathode right anterior, anode in nasal bone. Recording from left posterior to anterior (L21), left to right posterior (LR2), and left anterior to right posterior (L1R2). Upward deflection indicates negativity at first-named electrode of each lead. Note afterdischarge consisting of positive sharp waves from right posterior electrode, while only slow activity is seen on the unstimulated side. Only motor components of seizure were dilatation of pupils and ocular movements.

These preliminary observations with seizures induced by low frequency stimulation suggest some interesting possibilities for further study. The electroencephalogram and motor manifestations are not unlike those seen in some patients with psychomotor seizures. They remain relatively stereotyped and do not transform into major seizures over a wide range of stimulus voltages. They are relatively resistant in pattern to drug action, although their threshold may be raised. Electroencephalographic study suggests a cortical origin with slow secondary discharges

in parts of the cortex distant from the site of stimulation. Thus from several points of view it seems possible that a crude experimental equivalent of psychical seizures in man may be reproduced in animals by low frequency electroshock. If so, they should provide a useful background for the testing of anticonvulsant drugs effective against psychomotor seizures. Furthermore, they may provide some insight into the peculiarities of psychical attacks initiated by slowly discharging foci in trigger areas of the cerebral cortex.

DRUGS USED IN TREATMENT OF PSYCHIC SEIZURES

Clinical Evaluation

Rather than enumerate all the agents which have been reported occasionally useful in the treatment of psychomotor seizures, it would seem more profitable at this time to compare those few anticonvulsants which have seen enough clinical use to justify an evaluation of their therapeutic worth and sufficient experimental investigation to cast some light upon their mechanism of action.

Clinical experience[8, 72] and a survey of the literature suggest the following evaluation of effectiveness of the common antiepileptic drugs when used alone:

1. Phenurone: marked improvement in approximately half of otherwise refractory cases;
2. Mesantoin: effective in a smaller percentage of cases;
3. Diphenylhydantoin: occasional improvement, but often psychical seizures or aura become more obvious with suppression of major attacks;
4. Trimethadione: results vary from slight improvement to exacerbation;
5. Phenobarbital: rarely improvement, more often exacerbation.

In addition to these, amphetamine may be used with benefit in the control of behavior disorders associated with seizures, or may be added to prior effective antiepileptic medication to combat side effects without exacerbation of seizures. Among other drug combinations, trimethadione and diphenylhydantoin together may give results comparable to Mesantoin in psychomotor seizures. The addition of phenobarbital to other medication sometimes gives considerable improvement in spite of the ineffectiveness of phenobarbital alone.

Experimental Comparison

In the experimental investigation and assay of anticonvulsant drugs, a battery of tests has been employed which takes into account several aspects of drug action.[65, 71, 73] The relevant data for the drug series mentioned above is shown in table 1. Procedures are carried out on Sprague-

TABLE 1

PROTECTIVE INDICES OF SOME CLINICALLY USEFUL ANTIEPILEPTIC DRUGS BY FOUR DIFFERENT ASSAY METHODS IN RATS[65]

Antiepileptic	TD_{50}, *mg/kg i.p. or s.c.*	*Protective indices, TD_{50}/ED_{50}*				*Clinical use*
		Maximal electroshock seizure pattern	*Normal electro-shock threshold*	*Hydration electroshock threshold*	*Metrazol seizure protection*	
Phenurone	730	17.7	18.7	3.24	3.65	PS, GM, PM
Mesantoin	50	11.1	0.69	1.42	0.91	GM, PS
Diphenylhydantoin .	104	2.36	0	0.53	0	GM, PS
Trimethadione	445	1.23	1.51	1.17	1.48	PM
Phenobarbital	22	3.58	1.75	1.18	0.85	GM
Amphetamine	2.6	0.87	...	...	0	PM, behavior disorders

Dawley rats, the ED_{50} for single doses of the test agent being determined for the following criteria: (a) abolition of extensor component of supramaximally-induced electroshock seizures, (b) increase in threshold for minimal electroshock seizure in normal animals and (c) in rats previously hydrated, and (d) abolition of seizures induced by a standard dose of Metrazol. Since margin of safety rather than absolute potency is of clinical importance, the dose (TD_{50}) giving minimal central nervous signs is also determined, and is then divided by the various ED_{50} values to give corresponding protective indices for the several tests.

In addition to these standard tests in rats, peripheral nerve is used to determine the concentration required to abolish hyperexcitability and hyperresponsiveness induced by repetitive supramaximal stimulation or by excitant agents.[71] Electroencephalographic studies are carried out in rabbits with implanted epidural electrodes through which both stimulation and recording can be effected, so that changes in threshold and pattern of evoked convulsive and nonconvulsive responses can be studied.[23] Still in a preliminary stage of validation is a new test based on the ability of some anticonvulsant drugs to raise threshold for clonic or behavioral seizures in rats stimulated with 5/second shocks through corneal electrodes.

The results of the standard tests shown in table 1 give no clue to the comparative rank of this drug series in effectiveness against psychomotor seizures. It is apparent that ability both to modify seizure pattern and to raise threshold are factors in antipsychomotor effectiveness, but this hardly explains the poor clinical efficacy of phenobarbital. Obviously one must look for additional factors in the action of these drugs, and a more detailed description of their effects is therefore in order.

PHENURONE (phenacetylurea)

Clinical: The most extensive study of this new drug is that of Gibbs, Everett and Richards.[19] In a group of epileptic patients previously found refractory to other forms of medication, they found the greatest benefit in the psychomotor group (50 per cent greatly improved), although improvement was also found in the petit mal (46 per cent) and grand mal cases (33 per cent). The usual adequate daily dosage was 2.5 gm. and doses above 3.5 gm. were not further effective. Side actions in order of occurrence were exaggeration of personality disturbances, anorexia, feeling of weakness, headache, insomnia, palpitation, rash, urinary changes and jaundice.

In a smaller series of patients, Davis[5] has observed dramatic improvement in some cases of psychomotor seizures, but has seen no benefit of Phenurone alone in petit mal or grand mal. That the personality aberrations do not necessarily increase with suppression of the psychomotor attacks is illustrated by one case of an 11 year old boy with a history of typical psychomotor seizures associated with a temporal sharp-wave focus and a personality disturbance culminating in frequent episodes of fire-setting. Both seizures and behavior disorder were suppressed by Phenurone in a daily dose of 2.5 gm. On the other hand, Davis reports the development of acute psychosis requiring withdrawal of Phenurone in an adult female patient, despite improvement of psychomotor seizures. This patient also suffered dermatitis during Phenurone therapy. In two other cases toxicity necessitated withdrawal of Phenurone, one because of mild hepatitis with jaundice and another because of moderate neutropenia. Toxic effects disappeared in all three patients upon withdrawal of the drug. Davis finds no evidence of analgesic effects of Phenurone as described in a single case report by Forster and Frankel.[15]

Experimental: Phenurone was one of a series of conceivable degradation products of hydantoins synthesized by Spielman.[64] Everett[12] found it to be the most effective of a large number of agents tested against chemically and electrically induced seizures. Swinyard[65] reported that it excelled all of the substances hitherto assayed by the four standard methods (see table 1). Preliminary observations indicate that Phenurone is moderately effective in raising the threshold for partial seizures induced in rats and rabbits by low frequency electroshock, although the characteristic pattern of their seizures is not changed. High doses sufficient to produce incoordination in the rabbit modify the resting electroencephalogram in the direction of slow activity. The author[72] has found that Phenurone compares favorably with other acetylureas and hydantoins in

ability to suppress various types of induced hyperexcitability and hyperresponsiveness in peripheral nerve, the ED_{50} being 0.8 mMol/l. This concentration is the equivalent of a dosage of 28.5 mg./kg assumed to be distributed in extracellular fluid, or approximately the equivalent of a 2 gm. single dose in the adult patient. The aqueous solubility of Phenurone is only 3.12 mMol/l at body pH and temperature, setting an upper limit of approximately 8 gm. as the amount which can be absorbed and retained in the extracellular fluid of the adult human body, and possibly explaining both the clinical saturation effect noted by Gibbs et al.[19] and the apparently high protective indices noted by Swinyard.[65]

MESANTOIN (3-methyl-5, 5-phenyl-ethylhydantoin)

Clinical: The initial clinical trial of this agent by Loscalzo,[44] Kozol,[30] Clein[6] and Lennox[37] indicated that it could control many cases of grand mal and psychomotor seizures which were refractory to other medication. Marburg and Helfand[46] also reported favorable results in petit mal, but confirmation has not been forthcoming. More recently Kozol[31] has published results on a series of 200 patients given an average of 0.58 gm./day. Interpreting his findings, one can estimate approximately 80 per cent complete or almost complete remissions in patients with psychomotor seizures, and 70 per cent in those with grand mal. These results would excel those of Phenurone[19] if the data were comparable, but the Phenurone series reported by Gibbs and his associates seems to have consisted of more refractory cases.

Our own limited studies with Mesantoin show occasional dramatic remissions in major and psychomotor seizures, and one case of temporary benefit in an aberrant petit mal. Unlike diphenylhydantoin, Mesantoin seemed able to suppress cortical focal discharges as well as the secondary involvement manifested in the electroencephalogram. Results were particularly favorable with institutionalized grand mal cases with gross electroencephalographic pathology. It is of interest to note that Mesantoin can itself produce diffuse electroencephalographic abnormalities, chiefly of fast wave type, as recently reported by Little.[40]

The chief toxic side effect noted by Kozol[31] and others has been sedation. Morbilliform or scarlatinaform rashes have been seen in about 8 per cent of cases, and exfoliative dermatitis may occur.

Experimental: Tainter et al.[70] found Mesantoin highly effective in raising electroshock threshold in experimental animals. Swinyard and Goodman[66] noted that it was more effective than diphenylhydantoin in altering seizure pattern in experimental animals, and that it also was more effective in raising threshold for seizures induced by Metrazol or by

electroshock in normal or hydrated animals[65] (see table 1). The author and colleagues found that it resembled diphenylhydantoin in ability to modify human electroshock seizures.[74] Unlike diphenylhydantoin, it stabilizes peripheral nerve only in saturated concentrations.[72]

Swinyard et al.[67] have compared the isomeric forms of Mesantoin for anticonvulsant potency in rats. The levo, dextro and racemic forms are approximately equal in ability to modify maximal electroshock seizures, indicating that no precise spatial requirement is essential to this property. The levo form is approximately twice as potent as the dextro isomer in producing ataxia and also in ability to protect against Metrazol-induced seizures. Since therapeutic index rather than absolute potency is a primary clinical consideration, it might be inferred that the dextro isomer could safely be used in relatively larger doses. However, only clinical trial can determine whether the isomers differ in non-neurologic side effects, such as dermatitis and blood dyscrasias.

DIPHENYLHYDANTOIN (Dilantin; 5,5-diphenylhydantoin)

Clinical: The successful clinical trial of diphenylhydantoin by Putnam and Merritt[56, 57] established the important fact that an anticonvulsant need not have sedative properties. In addition to its superiority over phenobarbital and bromide in the treatment of grand mal,[49, 50, 51] diphenylhydantoin was also reported effective in the treatment of some cases of psychomotor epilepsy,[18, 36, 76] related behavior disorders[16, 58] and symptomatic epilepsies.[52] Not all investigators agree on its usefulness, however.[19] The dosage usually employed has been 0.3 to 0.5 gm./day. Ingestion of much larger doses has been reported without fatal outcome,[3] probably because of the limited solubility of the drug in the body (0.157 mM/L, or the equivalent of 0.6 gm. in the extracellular fluid of an adult man). The chief toxic effects reported for acute overdosage have been excitement with signs of vestibular involvement, and, for chronic overdosage, gingival hyperplasia and hyperkeratosis. In our experience, an interesting effect of diphenylhydantoin has been to suppress diffuse electroencephalographic dysrhythmia without suppressing the activity of the primary focus. This restricting action is also seen clinically in the reduction of major seizures without obliteration of the aura or prodrome, and is most strikingly seen with psychomotor seizures associated with occasional grand mal attacks.

Experimental: The experimental actions of diphenylhydantoin have been previously discussed in some detail.[71, 73] Although it was introduced for clinical trial by Putnam and Merritt on the basis of its apparent superiority in raising electroshock seizure threshold in cats,[56] the author

and his colleagues have found that diphenylhydantoin has little effect upon threshold for minimal electroshock seizure or those induced by Metrazol. However, it elevates toward normal the threshold lowered by hydration[69] or by excess phosphate ion.[77] The chief characteristic of diphenylhydantoin is its ability to abolish the tonic component of electroshock seizures in animals[75] and in man[74] without other overt effects upon the central nervous system. Evidence from nerve studies[71] indicates that diphenylhydantoin in relatively low concentration (0.05 mM/l) can stabilize neuronal membranes against lowering of threshold and high frequency discharge of impulses induced by repetitive supramaximal stimulation or by excess of phosphate ion. This action is apparently related to an effect upon one of the lipid components of nerve, as judged by the ability of the drug to modify the uptake of radioactive P^{32} into the various fractions of nerve tissue.[14] In general the experimental studies with diphenylhydantoin suggest a threshold-stabilizing rather than a threshold-raising mechanism of action, and lead to the conclusion that the drug is clinically useful because of its ability to prevent spread of seizure activity rather than to abolish primary seizure discharges.

TRIMETHADIONE (Tridione; 3,5,5-trimethyl-oxazolidine-2,4-dione)

Clinical: Despite its great value in suppressing seizures of the petit mal triad,[9, 23, 35, 38, 55, 60] trimethadione has not been found uniformly effective in the treatment of psychomotor seizures. Some investigators report favorable results,[10, 61] while others find little or no benefit with trimethadione alone.[38, 48] Part of the disagreement seems to revolve around the definition of psychomotor attacks. In the author's experience, the favorable effects of trimethadione alone are not limited to petit mal, but are manifest in those types of seizures which are hyperventilation-sensitive and occur with an abrupt onset.[72] The latter feature is in direct contrast to the action of diphenylhydantoin which seems to be primarily effective in limiting the spread of progressively developing seizure patterns. The combination of the complementary action of both drugs sometimes gives impressive clinical results in cases where neither drug alone is adequate,[4] and this action extends to psychomotor seizures,[9, 23] in which the results are comparable to those with Mesantoin.[8]

The usual dosage range for trimethadione alone or in combination is from 0.6 to 1.5 gm./day. The undesirable side effects include sedation[55] and hemeralopia.[38, 62] Occasional severe dermatitis and blood dyscrasias[38] necessitate withdrawal of the drug, in which case the closely related Paradione can sometimes be substituted successfully.[9, 11] Seizures may be exacerbated during the first few days of therapy,[23, 38] leading to an un-

favorable estimate of drug efficacy, since an early exacerbation may be followed by complete remission of attacks without change in dosage.[23] In addition to these undesirable actions, trimethadione has also been reported to produce analgesia.[59]

Experimental: Spielman[63] first reported trimethadione as an experimental analgesic, and it was subsequently shown by Everett and Richards[13] to raise threshold for both electrically and chemically-induced seizures. The author and his colleagues found trimethadione relatively poor in ability to modify maximal seizure pattern in animals and man,[74, 75] and observed that the outstanding property of this drug was its protective action against Metrazol-induced seizures and subconvulsive electroencephalographic phenomena. It also raised electrical thresholds for evoked convulsive and nonconvulsive discharges, and in large doses produced a sleep-like electroencephalographic record similar to that seen with barbiturates. Trimethadione was found to have a depressant action upon peripheral nerves only in relatively high concentration (30 mM/kg).

Loewe[43] has found a high degree of synergism between trimethadione and diphenylhydantoin in their ability to modify experimental seizure pattern, a relationship which may help to explain the relatively greater effectiveness of the combination over either drug alone.

PHENOBARBITAL (5,5-phenylethyl barbituric acid)

Clinical: In 1912 Hauptman reported that phenobarbital was superior to bromide in the treatment of grand mal, and for a quarter of a century it remained the most effective clinical anticonvulsant until superseded by diphenylhydantoin in 1938. It has been generally found useless in the treatment of psychic seizures, sometimes making them more frequent.[34] The usual effective dosage is in the neighborhood of 0.1 gm./day. The principal side effect is sedation. One of the disadvantages of phenobarbital not usually found in other anticonvulsants is an increase in frequency of seizures or their appearance *de novo* upon abrupt withdrawal of the drug.[29] A minor inconvenience is the occurrence of diffuse electroencephalographic changes, usually fast waves, with therapeutic dose levels.[32]

Experimental: Like other barbiturates, phenobarbital raises the threshold for electrical excitation of the brain, but it excels the nonanticonvulsant barbiturates in ability to modify maximal electroshock seizure pattern and to stabilize thresholds in peripheral nerve; in experimental anticonvulsant properties it lies somewhat intermediate between diphenylhydantoin and trimethadione.[73] It resembles other barbiturates in prolonging recovery time of cerebral neurones,[27, 47] a general feature in the sedative action of barbiturates. The author has noted exacerbation of

sharp wave discharges from epileptogenic lesions in the cerebral cortex of the rabbit with subsedative doses of phenobarbital.[72] Apparently the slowing of recovery time and the tendency toward hypersynchronization of cortical rhythms may override the threshold-raising ability of phenobarbital, permitting focal discharges to occur uninhibited.

AMPHETAMINE

Clinical: Amphetamine (Benzedrine) and more recently the active dextro isomer (Dexedrine) have been used chiefly to combat the sedative effects of antiepileptics such as trimethadione and phenobarbital. However, they have been used alone successfully in the therapy of petit mal,[22, 41] and in the treatment of behavior disorders associated with electroencephalographic abnormalities or with clinical seizures,[5, 7, 39] usually in children. The tendency of amphetamine to accelerate and desynchronize the electroencephalogram is of interest.[21, 39] With the usual daily doses of 20 mgm. of amphetamine (or 10 mg. of the dextro isomer) used in children, the characteristic side effects include anorexia, increased emotional tension and insomnia.[5] It would be of interest to determine whether amphetamine can reduce the exaggerated personality disturbances seen in psychomotor patients under treatment with Phenurone,[19] without loss of the antiepileptic effect of this drug.

Experimental: Although capable of antagonizing the effects of depressant anticonvulsants, amphetamine by itself does not have the convulsant properties of Metrazol and related analeptics, and fails to produce hypersynchronized bursts of Metrazol type in the electroencephalogram of the rabbit.[72] Amphetamine has minimal effects on cortical thresholds, and does not abolish the threshold-raising action of phenobarbital. In excitant doses (3.0 mg./kg), it may modify maximal electroshock seizure pattern in the rat in a manner similar to that of the anticonvulsants. It has been shown to increase the rate of postseizure recovery and to diminish the postictal slow wave abnormalities.[33] Amphetamine can compensate to a considerable degree for experimental neurologic deficits resulting from central nervous lesions,[45] possibly by replacing, through increased internuncial activity, the loss of facilitation from the centers destroyed.

DISCUSSION

The preceding survey is somewhat disappointing in that it fails to indicate any obvious features of drugs active against psychomotor epilepsy which are not also to be found in some of the ineffective agents. The effectiveness of Phenurone, Mesantoin and the trimethadione-diphenyl-

TABLE 2

DOSAGES OF 5,5-PHENYL-R-HYDANTOINS (HYD) AND ACETYLUREAS (AC) REQUIRED FOR ANTICONVULSANT ACTION IN RATS,[68] AND CONCENTRATIONS REQUIRED FOR STABILIZATION OF THRESHOLD IN FROG SCIATIC NERVE[72]

	I	II	III	IV	V	VI	VII	VIII	IX
R	H	H	CH_3	CH_2	C_2H_5	C_2H_5	C_6H_5	C_6H_5	$(CH_3)_2$
Group	ac	hyd	ac	hyd	ac	hyd	ac	hyd	ac
Solubility mM/L @ 37°C	3.12	14.3	3.64	17.4	1.63	5.35	0.053	0.157	3.81
Rat: oral dose, mg/kg									
(a) CNS signs	740	1620	173	332	170	119	>1600	>3200	165
(b) Electroshock test	40	170	17.5	16.0	18.0	10.8	>1600	30	38
(c) Metrazol test	212	>1600	59	203	160	62	>1600	>3200	44
Frog sciatic nerve: mM/L									
(d) Rebound spike	0.8	1.0	1.9	1.0	0.2	1.0	>sat	0.05	0.5
(e) Facilitation	0.8	1.0	0.9	0.7	0.8	0.5	>sat	0.2	0.5
(f) Phosphate firing	0.8	1.0	0.7	0.7	0.2	0.7	>sat	0.02	1.0
Clinical use	PS GM PM	—	—	GM PS	GM	chorea	—	GM PS	PM

Doses are those required in 50 per cent of tests for (a) production of minimal neurological toxic signs, (b) abolition of extensor tonic component of maximal electroshock seizure, (c) prevention of seizures induced by Metrazol 70 mg/kg s.c., (d) prevention of repetitive firing and (e) of threshold lowering produced by repetitive supramaximal shocks, and (f) prevention of repetitive firing induced by isotonic phosphate solution. Compounds which have received clinical use are I. Phenurone,[8, 19] IV. Phenylmethylhydantoin,[49] V. Phenylethylacetylurea,[8] VI. Nirvanol,[31] VIII. Diphenylhydantoin,[50] IX. Phenyldimethylacetylurea.[8]

hydantoin combination suggests that both the threshold-raising and spread-preventing features of anticonvulsant action are necessary to adequate therapy. The lack of sedative action of Phenurone in therapeutic dosage may be a factor giving this drug an advantage over some other forms of medication.

The success of Phenurone invites further research in the anticonvulsant properties of other acetylureas, a drug group of which many examples have now been synthesized and given preliminary tests.[64] Alteration of structure in this group does not give a series of compounds strictly analogous with the corresponding hydantoins, as may be seen from table 2.

The development of tests having greater relevance for antipsychomotor activity, such as the low frequency electroshock test described in this report, may offer a new method of attack in the search for better therapy. But since the final validation must be made upon patients it

would be advantageous to have a more rigorous classification of the convulsive disorders, particularly with regard to their electroencephalographic classification as well as to their focus of origin. Thus it would be desirable to know whether all seizures having in common slowly repeated cortical focal sharp wave discharges from a common therapeutic group, or whether there is a greater uniformity in response to therapy when, for example, all seizure of anterior temporal lobe origin are analyzed together. This type of clinical information would do much to point out new methods for experimental analysis and accelerate progress toward better therapy.

SUMMARY

1. A possible mechanism of psychic seizures is described, based on observations in man and experimental animals. It is suggested that cortical epileptogenic lesions favorably situated to produce slow repetitive discharges may disrupt the function of the remaining normal cortex by hypersynchronized bursts of impulses which are too slow in frequency to produce complete spread of true seizure activity.
2. The experimental production of seizures dependent upon this mechanism is discussed.
3. Some clinical and experimental features are described for the antiepileptic agents which have been used with varying degrees of success in the treatment of psychomotor seizures.
4. Data is presented on the experimental anticonvulsant actions of some acetylureas and the corresponding hydantoin compounds.

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Second Attacks of Acute Anterior Poliomyelitis

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FROM time to time observers have noted patients who, during the convalescent phase of poliomyelitis, exhibit a recurrence of acute systemic symptoms, in conjunction with an extension of paralysis to myotomes previously unaffected. This situation has been noted weeks, and sometimes months, after the initial phase of the disease. Since man is known to harbor the poliomyelitis virus in his nasopharyngeal secretions and/or gastrointestinal tract as a convalescent carrier for many months following the acute phase of the disease, progression or development of additional paralysis during this period is considered a recrudescence of the original infection.

Still[1] and Cohen[2] recognized two types of recurrence of poliomyelitis: (1) those occurring during the first three or four months after the initial infection were considered a recrudescence; (2) those appearing two or more years later were considered a re-infection.

Unquestionably, second attacks of acute anterior poliomyelitis are rare. In past years some observers have maintained that such instances do not occur. The first report of such a case was reported by Caudouin in 1879.[3] Fischer and Stillerman[4] in 1938 collected 13 cases from the literature, added four of their own, and cited four others, previously unrecorded, from different observers. In 1948, Fox, et al., summarized 36 cases, 14 of which were considered doubtful.[5]

Data on all reported cases of second attacks, i.e., those occurring two or more years after the first infection, are presented in table 1. Those cases marked with an asterisk have been considered by others[2, 4, 5] as doubtful cases because of insufficient clinical evidence or incompleteness of the records. The remaining 25 cases, as well as the one to be presented here, satisfy diagnostic criteria sufficiently to be considered authentic.

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TABLE 1

Case No.	*Author and Date of Report*	*Age at Time of Attacks*	*Interval*	*Parts Affected*
1.*	Caudouin 1879[3]	1) 17 mos. 2) 16 yrs.	14 yrs.	1) rt. leg 2) lt. leg
2.*	Ballet & Dutil 1884[6]	1) 3 yrs. 2) 12 yrs. 3) 14 yrs.	9 yrs. 2 yrs.	1) lt. leg 2) arms 3) legs
3.*	Eshner 1910[7]	1) 2 yrs. 2) 13½ yrs.	11 yrs.	1) rt. lower 2) weakness both hands
4.	Eckert 1911[8]	not given	5½ yrs.	1) lt. leg 2) rt. leg
5.*	Culmont & Baudouin 1911[9]	1) 60 yrs.	1 yr.	1) flaccid paralysis arms and legs with recovery 2) flaccid paralysis arms and legs with death
6.	Lucas & Osgood 1913[10]	1) 2 yrs. 2) 5 yrs.	3 yrs.	1) both feet and rt. leg 2) rt. arm and both legs
7.*	Sanz 1915[11]	1) 1 yr. 2) 15 yrs.	14 yrs.	1) lt. leg 2) rt. leg
8.*	Taylor 1916[12]	1) 3 yrs. 2) 6 yrs.	3 yrs.	1) rt. leg and arm 2) lt. leg
9.*	Sheppard 1916[13]		16 yrs.	1) lower extremities 2) hands, lowers, abdomen acute ascending paralysis
10.*	Francis & Moncrieff 1919[14]	1) 3 yrs. 2) 18 yrs.	15 yrs.	1) upper extremities 2) lower extremities
11.*	Permeans 1923[15]	1) 2¾ yrs. 2) 4¾ yrs.	2 yrs.	1) lt. leg 2) lt. arm
12.	Still 1930[1]	1) 1¾ yrs. 2) 7½ yrs.	5¾ yrs.	1) lt. leg 2) rt. shoulder
13.	Neal 1932[16]	1) 4 yrs. 2) 8 yrs.	4 yrs.	1) rt. leg 2) rt. leg
14.	Neal 1932[16]	1) 16 mos. 2) 21 yrs.	20 yrs.	1) both lowers 2) lt. thigh
15.*	Quigley 1934[17]	1) 5 yrs. 2) 7 yrs.	2 yrs.	1) lt. shoulder 2) bulbospinal type
16.*	Moore 1934[18]	1) 10 mos. 2) 7 yrs.	6 yrs.	1) lower extremities 2) hands, lowers, abdomen
17.	Tesdal 1934[19]	1) 16 yrs. 2) 40 yrs.	24 yrs.	1) both legs 2) both arms
18.	Cohen 1935[2]	1) 6 yrs. 2) 31 yrs.	25 yrs.	1) rt. arm and leg 2) lt. arm and leg
19.	Cohen 1935[2]	1) 12 yrs. 2) 30 yrs.	18 yrs.	1) rt. arm and lowers 2) arms, legs, trunk
20.	Bolzinger & Falconnet 1936[20]		14 yrs.	1) not given 2) paralysis of one extremity, paresis of another
21.	Nielson 1938[21]	1) 9 mos. 2) 30 yrs.	29 yrs.	1) both legs 2) both legs and trunk
22.	Casaubon & Cossey 1935[22]		2 yrs.	1) upper and lower extremities 2) upper and lower extremities

TABLE 1 (Cont'd)

Case No.	*Author and Date of Report*	*Age at Time of Attacks*	*Interval*	*Parts Affected*
23.	Neal and others personal communication cited by Fischer & Stillerman 1938[4]		9 yrs.	1) lt. arm 2) no paralysis
24.	Neal, Josephine B.: Poliomyelitis (Survey of International Committee) cited by Fischer & Stillerman 1938[4]		6 yrs.	1) rt. leg 2) lt. leg
25.	du Busc, L. C. V.: Personal communication cited by Fischer & Stillerman[4]		8 yrs.	1) both legs 2) bulbar type
26.	Neal and others personal communication cited by Fischer & Stillerman 1938[4]	1) 9 yrs. 2) 14 yrs.	5 yrs.	1) rt. shoulder and rt. leg 2) rt. thigh and lt. external rectus
27.	Neal and others personal communication cited by Fischer & Stillerman 1938[4]	1) 9 yrs. 2) 13 yrs.	4 yrs.	1) rt. lower extremity 2) non-paralytic
28.	Neal and others personal communication cited by Fischer & Stillerman 1938[4]	1) 3 yrs. 2) 7 yrs.	4 yrs.	1) non-paralytic 2) bulbar type, rt. upper, death
29.	Fischer & Stillerman 1938[4]	1) 4½ yrs. 2) 6½ yrs.	2 yrs.	1) rt. leg 2) rt. leg and thigh, lt. thigh, upper abdomen
30.*	Harmon, P. H.: Personal communication cited by Fischer & Stillerman[4]		8 yrs.	1) both legs 2) one arm, both legs
31.*	Harmon, P. H.: Personal communication cited by Fischer & Stillerman[4]		17 yrs.	1) one leg 2) one arm, both legs
32.	Neal, Josephine B.: Poliomyelitis (Survey of International Committee) cited by Fischer & Stillerman 1938[4]		20 yrs.	1) both legs 2) left thigh
33.*	Toomey 1938[23]	1) 3 yrs. 2) 20 yrs.	17 yrs.	1) lower extremities 2) upper and lower extremities
34.	Nelson & Green 1943[24]	1) 4 yrs. 2) 9 yrs.	5 yrs.	1) legs, abdomen and back 2) abdomen and back
35.	Nelson & Green 1943[24]	1) 4 yrs. 2) 6 yrs.	2 yrs.	1) arms 2) legs
36.	Nelson & Green 1943[24]	1) 10 mos. 2) 9 yrs.	8 yrs.	1) lt. leg 2) lt. arm
37.	Nelson & Green 1943[24]	1) 10 yrs. 2) 14 yrs.	4 yrs.	1) lt. leg 2) bulbar
38.	Wyllie 1945[25]	1) 18 yrs. 2) 32 yrs.	13 yrs.	1) rt. calf weakness 2) both legs and lumbar muscles
39.	Bissell 1946[26]	1) 30 yrs. 2) 31 yrs.	16 mos.	1) lt. arm, rt. leg 2) both arms, bulbar and respiratory paralysis, death, P.M. polio
40.*	Bridge et al. 1946[27]	1) 9 yrs. 2) 27 yrs.	18 yrs.	1) lt. leg 2) ? lt. leg

TABLE 1 (Cont'd)

Case No.	Author and Date of Report	Age at Time of Attacks	Interval	Parts Affected
41.*	Bridge et al. 1946 [27]	1) 6 yrs. 2) 17 yrs.	11 yrs.	1) lt. leg 2) ? lt. leg
42.*	Bridge et al. 1946[27]	1) 3 yrs. 2) 15 yrs.	12 yrs.	1) both legs 2) both legs
43.*	Bridge et al. 1946[27]	1) 8 yrs. 2) 11 yrs.	3 yrs.	1) non-paralytic 2) both arms
44.*	Bridge et al. 1946[27]	1) 15 yrs. 2) 19 yrs.	4 yrs.	1) paresis both arms and legs 2) non-paralytic
45.*	Bridge et al. 1946[27]	1) 2 yrs. 2) 7 yrs.	5 yrs.	1) non-paralytic 2) one arm, both legs
46.	Aubin-Figueroa et al. 1946[28]	1) 20 mos. 2) 4½ yrs.	2½ yrs.	1) lt. upper 2) lt. VII N. and lowers
47.	Alves & Pugh 1947[29]	1) 3½ yrs. 2) 12 yrs.	8½ yrs.	1) lt. face 2) rt. leg
48.	Ashley 1947[30]	1) 10 yrs. 2) 16 yrs.	6 yrs.	1) rt. thigh 2) rt. arm and hand
49.	Fox, Madden & Kohn 1948[5]	1) 7 yrs. 2) 8 yrs.	1 yr.	1) spinal type 2) bulbar type

*Patients considered by previous authors[2, 4, 5] as doubtful cases because of insufficient data.

PRESENTATION OF CASE

The following case is that of a man who sustained a second attack after an interval of 24 years.

The patient, a man aged 39, was first seen at the University Hospital in July 1932. At that time he was 22 years of age and complained of weakness in the left arm and leg. It was found that at age 15, during a local epidemic of poliomyelitis, he had an acute illness characterized by nausea, severe occipital headache and fever of 102° F. Two days after the onset, he developed weakness of the left shoulder girdle, left arm and both legs. During the following days he improved gradually, but was left with a residual weakness of the involved members.

When examined in 1932, the patient was able to walk with the aid of two canes. Both peroneal muscle groups were weak, but the left side was more severely involved. The left quadriceps group was weak and flaccid. The circumference of the left thigh at its midpoint was 32 cm., in contrast to the measurement of 42 cm. for the right thigh. The patellar reflex was absent on the left. Slight weakness of the trunk musculature was evident, and the patient exhibited a dorsal scoliosis to the right. Atrophy and weakness of the left shoulder girdle were present, together with weakness and slight wasting of the left biceps and triceps muscles. The sensory examination failed to disclose any abnormalities. These findings were interpreted as representing the residual manifestations of acute poliomyelitis which occurred at the age of 15 years. Subsequently the patient had a triple arthrodesis of the left ankle, after which he was able to work regularly as a radio engineer, at times devoting as many as 12 hours a day to his occupation.

On November 9, 1949, this patient complained of malaise and weakness. Two days later he developed a severe occipital headache, backache and fever of 102° F. During the second day of his illness he developed weakness of the right lower ex-

tremity, particularly of the thigh region. The spinal fluid examination disclosed 74 cells per cubic millimeter (82 per cent lymphocytes and 16 per cent polymorphonuclear leucocytes). The total protein value of the fluid was 56 mg. per 100 ml. Six days after the onset of his initial symptoms, the patient was transferred to the isolation service of the University Hospital.

His temperature was 100° F. and his pulse rate was 95 per minute. He appeared acutely ill. Attempted anteflexion revealed extreme stiffness of his neck. Considerable tenderness of the right anterior thigh musculature was noted. The weakness, atrophy and reflex changes observed in 1932, particularly in the left upper and lower extremities, were substantiated. Additional changes in the form of paresis and flaccidity without muscle atrophy were now apparent in the flexors and extensors of the fingers, wrist, forearm and arm on the right side. New findings were evident in the flexors and extensors of the right lower extremity. The details are presented in the accompanying muscle chart. Examination of the deep tendon reflexes now showed that the left biceps reflex could scarcely be elicited. The right triceps reflex was diminished, and both patellar reflexes were absent. No pathologic reflexes were observed, and no sensory deficit could be detected.

The urinalysis disclosed no albumin or sugar. The hemoglobin value of the blood was 13.5 gm. The erythrocytes numbered 4,950,000 and the leucocytes 12,200 per cubic millimeter. The differential of the blood smear showed 67 per cent segmented polymorphonuclear leucocytes, 2 per cent eosinophils, 2 per cent basophils, 25 per cent lymphocytes and 4 per cent monocytes. Serologic tests on the blood for syphilis were negative. The second spinal fluid examination disclosed clear fluid under normal initial pressure, 16 lymphocytes per cubic millimeter, a negative globulin test, a total protein value of 48 mg. per 100 ml. and a chloride content of 775 mg. per 100 ml. The spinal fluid Wassermann was negative. Neutralization tests performed on the blood serum for the presence of eastern and western equine encephalomyelitis and St. Louis encephalomyelitis were negative.

During his hospital stay the patient showed slight improvement, and by the time of discharge he was able to walk with the aid of crutches. Since that time, his course has remained essentially unchanged.

MUSCLE CHART*

First Attack				*Second Attack*	
Rt.	*Lt.*	*Action to be Tested*	*Muscle*	*Rt.*	*Lt.*
		Flexion of neck	Profundi colli	4	3
		Extension of neck	(sternocleidomastoid and		
	3	Rotation of neck	trapezius also		
		Lateral bending of neck	participate		3
		Elevation of upper thorax inspiration	Scaleni and diaphragm		
	4	Adduction of arm from behind to front	Pectoralis major and minor		4
	3	Forward thrust of shoulder	Serratus anterior	4	4
		Elevation of scapula	Levator scapulae	4	
	3	Medial adduction and elevation of scapula	Rhomboidei		3
		Abduction of arm	Supraspinatus		
		Lateral rotation of arm	Infraspinatus		
		Medial rotation of arm	Latissimus dorsi		
	3	Adduction of arm from front to back	Teres major, and subscapularis		

MUSCLE CHART*

First Attack Rt.	First Attack Lt.	Action to be Tested	Muscle	Second Attack Rt.	Second Attack Lt.
3		Abduction of arm	Deltoid		
		Lateral rotation of arm	Teres minor		
3		Flexion of forearm	Biceps brachii		
		Supination of forearm		4	2
		Adduction of forearm	Coracobrachialis		
3		Flexion of forearm	Brachialis	4	2
3		Pronarion of forearm Extensors	Pronator teres Triceps	1	2
		Radial flexion of hand	Flexor carpi radialis		
		Flexion of hand	Palmaris longus		
2		Flexion of middle phalynx of { index finger / middle finger / ring finger / little finger }	Flexor digitorum sublimis		2
		Flexion of hand		2	
		Flexion of terminal phalynx of thumb	Flexor pollicis longus		
		Flexion of terminal phalynx { index finger / middle finger }	Flexor digitorum profundus	2	
		Flexion of hand			
		Abduction of metacarpal of thumb	Abductorpollicis brevis		
		Flexion of proximal phalynx of thumb	Flexor pollicis brevis		
		Opposition of metacarpal of thumb	Opponens pollicis		
		Flexion of proximal phalynx and extension of the two distal phalynges of	{ index finger — lumbricales; middle finger — 2 lateral; ring finger — lumbricales; little finger — 2 medial }		
		Ulnar flexion of hands	Flexor carpi ulnaris		
		Flexion of terminal phalynx of { ring finger / little finger }	Flexor digitorum profundus		
		Flexion of hand			
		Adduction of metacarpal of thumb	Adductor pollicis		
		Abduction of little finger	Adductor digiti quinti		
		Opposition of little finger	Opponens digiti quinti		
		Flexion of little finger	Flexor digiti quinti brevis		
		Flexion of proximal phalynx extension of two distal phalynges adduction and abduction of fingers	Interossei	3	3
		Extension of forearm	Triceps brachii and anconaeus	1	2
		Flexion of forearm	Brachio radialis	4	2
		Radial extension of hand	Extensor carpi radialis		
		Extension of phalynges of { index finger / middle finger / ring finger / little finger }	Extensor digitorum communis	4 4 4 4	
		Extension of hand		4	
		Extension of phalynges of little finger	Extensor digit quinti proprius		
		Extension of hand		4	
		Ulnar extension of hand	Extensor carpi ulnaris		
		Suppination of forearm	Supinator		
		Abduction of metacarpal of thumb	Abductor pollicis longus		
		Radial extension of hand			
		Extension of thumb	Extensor pollicis brevis and longus		

MUSCLE CHART*

First Attack Rt.	First Attack Lt.	Action to be Tested	Muscle	Second Attack Rt.	Second Attack Lt.
		Radial extension of hand			
		Extension of index finger	Extensor indicis proprius	4	
		Extension of hand			
		Elevation of ribs			
		Depression of ribs	Thoracis, abdominis and dorsi		
	3	Contraction of abdomen			
		Anteroflexion of trunk		2+	
	3	Lateral flexion of trunk		2+	
	3	Dorsal flexion of trunk			
	2	Flexion of hip	Iliopsoas	3+	2+
	2	Flexion of hip	Sartorius	4	4
	1	Extension of leg	Quadriceps femoris	2	2
			Pectineus		
			Adductor longus		
	2	Adduction of thigh	Adductor brevis		
			Adductor magnus		3
			Gracilis		
		Adduction of thigh	Obturator externus		
		Lateral rotation of thigh			
	3	Abduction of thigh	Gluteus medius et minumus	3	2
	2	Flexion of thigh	Tensor fasciae latae	3	0
		Lateral rotation of thigh	Pyriformis		
	3	Abduction of thigh	Gluteus maximus		
			Obturator internus		
		Lateral rotation of thigh	Gemelli		
			Quadratus femoris		
			Biceps femoris	0	4
		Flexion of leg	Semitendinosus		
			Semimembranosus		
0	0	Dorsal flexion of foot	Tibialis anterior	0	
		Supination of foot			
	0	Extension of four lateral toes	Extensor digitorum longus		
		Dorsal flexion of foot		3	1
	0	Extension of great toe	Extensor hallucis longus		
		Dorsal flexion of foot		3	0-1
		Extension of great toe and medial three toes	Extensor digitorum brevis		1
	0	Plantar flexion of foot in pronation	Peronei	3	3
2	4	Plantar flexion of foot in supination	Tibialis post.		
	4	Plantar flexion of foot in supination	Triceps surae	1	3
		Flexion of terminal phalynx of toes II-v	Flexor digitorum longus	4	3
				0	0
		Plantar flexion of foot in supination	Flexor hallicus longus		
1	4	Flexion of terminal phalynx of great toe			
	4	Flexion of middle phalynx of toes II-v	Flexor digitorum brevis	2	2
		Flexion of proximal phalynx of great toe	Flexor hallucis brevis	2	2
		Spreading and closing of toes	Plantarres pedis relinqui		
		Flexion of proximal phalynx of toes			

*The following system of grading muscle strength was utilized: 4—good; 3—fair; 2—poor; 1—trace; 0—absent. Those muscles not tabulated were not listed in the case record and are therefore assumed to have been normal.

DISCUSSION

Although the authors did not observe this patient during the initial episode of his illness, the clinical record is sufficiently accurate to leave no doubt that the illness of 1932 was that of acute poliomyelitis. The second episode, observed in part by the authors, was unquestionably another attack of poliomyelitis, one which had occurred 24 years after the first and which added to the disability of this patient.

The observation that there are multiple strains of antigenically different poliomyelitis virus has been recorded by Trask, et al.,[31] Kessel, et al.,[32] and Paul and Trask.[39] Second attacks of the disease may reasonably be expected to occur. The occurrence of more than one attack has been demonstrated experimentally in monkeys by Kessel and Stimpert,[33] Howe and Bodian,[34] Toomey[35, 36, 37] and Flexner,[38] both by the use of homologous strains and by the use of heterologous strains.

However, many factors concerning immunity, crossed immunity, susceptibility to infection and the antigenic properties of the virus have eluded investigators so that the present state of our knowledge leaves many questions unanswered. Nevertheless, several possible explanations for the occurrence of several attacks of poliomyelitis are offered: (1) second attacks of poliomyelitis may be produced by a strain of virus antigenically unrelated to the one producing the initial infection; (2) certain strains may fail to stimulate tissue or humoral antibody production; (3) certain individuals may be incapable of antibody production; (4) the body may lose its immunity in the course of time and therefore be susceptible to reinfection with a homologous strain.

Any one, or any combination of these factors, may be held responsible for the occurrence of subsequent attacks of acute anterior poliomyelitis.

Repeated nonparalytic infections or abortive attacks of the disease may be quite common, especially in adults who have been in contact with others who have developed obvious clinical manifestations. It is quite likely that since man is continuously being exposed to the various strains of virus, a certain proportion seems to be particularly susceptible to reinfection.

SUMMARY AND CONCLUSIONS

1. To the 49 previously recorded cases of second attacks of accute anterior poliomyelitis summarized in table 1, is added one case observed by the authors.

2. The case reported here represents an instance of two distinct attacks, separated by an interval of 24 years.

3. Although admittedly rare, the occurrence of second attacks of paralytic poliomyelitis in the same individual is unquestionable.

4. The occurrence of additional symptoms, or extension of previously existing motor impairment during the few months immediately succeeding an initial attack of acute anterior poliomyelitis, should be considered a recrudescence of existing infection. New symptoms occurring two or more years after the initial episode should be considered a reinfection.

5. Factors responsible for the occurrence of second attacks of poliomyelitis are as yet little understood. However, several possible explanations are apparent, any one, or a combination of which may be operative in an individual case.

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Never has such an opportunity for the study of nerve lesions and their results presented itself. A multitude of cases, representing almost every conceivable type of obscure nervous disease, was sent to us from this department and that of Washington, by surgeons who felt conscious that these forms of disease were rarely amenable to treatment in wards crowded with grave wounds, constantly demanding all the time and care of overwork attendants.

Among these was a vast collection of wounds and contusions of nerves, including all the rarest forms of nerve lesion of almost every great nerve in the human body. Nor was this mass of material neglected in any point of view. New modes of treatment were devised, and gymnastic classes instituted, under the care of intelligent sergeants of the invalid corps; electricity was constantly employed and hypodermic medication—at that time somewhat novel—was habitually resorted to, and its effects carefully studied.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Aphasia: Effect of Intravenous Sodium Amytal

Philip S. Bergman, M.D. and Martin Green, M.D.

It is well known that patients with aphasia speak more easily when they are relaxed and have greater difficulty when anxious, tired or embarrassed. Reports have appeared describing improvement of aphasia after intravenous administration of sodium Amytal. It has been suggested that Amytal removes the inhibiting effect of anxiety usually present in patients with aphasia, thereby resulting in improved language function. For this reason, the effect of intravenous sodium Amytal was studied in 27 patients with aphasia.

MATERIAL AND METHOD

The subjects were 27 consecutive aphasic patients on the neurologic and medical services. There was no special selection of patients. Everyone regarded as aphasic by the neurologic or medical staffs was studied. Several patients who were found not to be aphasic after careful testing and a few moribund or otherwise highly uncooperative patients were not included. All degrees of aphasia were included, however, even those totally without speech.

All patients had disease of the brain. The diagnoses included cerebral vascular disease, cerebral neoplasm, degenerative brain disease, hypoglycemic encephalopathy, subdural hematoma, parenchymatous neurosyphilis and encephalopathy of undetermined cause.

A complete aphasic study was carried out a day or two before Amytal was administered, and was repeated just before the injection, with emphasis on the defects observed previously, in an effort to evaluate possible spontaneous variation. The patient was tested again during and immediately after administration of the drug. Thus, at least three exami-

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nations were given by each observer. Some patients had as many as 12 complete tests. Each interview usually lasted one-half hour to one hour. Since the tests were almost identical, the effect of learning, if any, would have been to improve successive performances. In view of the results obtained, this factor was disregarded.

Two observers examined the patients separately, and the results of each study were not known to the other until both had completed their examinations. When there was a difference in the results the study was repeated. This occurred in only two instances, and the difference could not be substantiated on further testing.

A 2.5 per cent solution of amobarbital sodium (sodium Amytal) was injected into an arm or hand vein, usually at the rate of 15 mg. per minute, the examination being continued throughout the injection. The appearance of nystagmus was taken as the first objective sign of barbiturate effect, and when this was observed testing was repeated. After the initial examination, the injection was continued in many cases until 0.25 or 0.5 gm. had been given. All responses to the tests were recorded verbatim in writing, insofar as possible, and many were preserved on phonograph records.

Some patients, particularly those in whom the clinical picture was changing, were tested in this way several times. Some were tested repeatedly over the course of several months.

The aphasia examination tested the following functions: (1) orientation; (2) indication of parts of the patient's body, on either oral or written command; (3) naming of parts of examiner's body; (4) following simple commands and complicated commands involving midline crossing; (5) naming objects and picking them from a group; (6) repeating words, sentences and numbers; (7) recognizing a common tune and whistling or singing in imitation; (8) naming colors and selecting them from a group; (9) reciting the days of the week, months of the year and the alphabet; (10) calculation; (11) spelling; (12) reading (letters, words, sentences, paragraph, numbers); (13) association of words with pictures; (14) recognition of symbols; (15) writing, spontaneously and from dictation; (16) copying; (17) executing simple and complicated motor acts in imitation or on command; (18) telling time.

RESULTS

Most patients gave surprisingly consistent responses from interview to interview during the many periods of testing prior to administration of sodium Amytal. Some, however, showed spontaneous fluctuations in performance. This was manifested by either poorer or better performance on

certain test items and occurred during a single interview or from one interview to the next.

The administration of sodium Amytal by the method described did not improve the speech of any patient in this series over periods of observation ranging from a few weeks to several months.

There was no change in aphasia at the point where nystagmus appeared or at any time up to this point. The amount of the drug necessary to produce nystagmus varied from 25 to 360 mg.; in addition to this wide variation from patient to patient, the same patient often required different amounts of drug from time to time. When the injection was continued past the point of nystagmus, the aphasia almost always became worse. It was invariably worse when the injection was carried to the point of "drunkenness." The following case exemplifies the change with increasing amounts of Amytal:

A woman 50 years of age had undergone subtotal removal of a large olfactory groove meningioma. At the time of testing she was alert, ambulatory and cooperative. She had mild aphasia, manifested principally by inability to name objects, and frequent spontaneous errors in speech. Some errors were made in reading a short newspaper article aloud, but they were corrected when the examiner pointed them out. However, she was completely unable to give the meaning of a printed paragraph. When she missed a word and substituted another, she often resorted to fantastic confabulation to justify the substitution. There were memory defects and at times mild disorientation.

Approximately 200 mg. of sodium Amytal was administered intravenously on two occasions. Up to the point of appearance of nystagmus (150 mg.) no change in the aphasia was noted; when more of the drug was injected she became drowsy and made many errors in spontaneous speech, naming of objects and reading. She also confabulated more freely. When re-examined two hours later she was less drowsy and made fewer errors in naming objects and in reading. The inability to read while under Amytal was particularly striking in contrast to her performance prior to the drug.

The effect of Amytal was the same regardless of the type of aphasia. Representatives of all the usual types were included, although on careful testing most of the patients were found to have a so-called "mixed" aphasia, with particular elements predominating.

The degree of disability and the progress of the aphasia were considered as possible factors influencing the response to Amytal. Included in the series were patients whose central nervous system disease was advancing, improving or stationary. There was no difference in the response to Amytal among these three groups.

Several patients were told that the injection would improve their speech. During administration of Amytal they reported that they seemed to be talking more easily and that they had made fewer errors, but in no instance could this impression be confirmed on testing. One of these

patients who had cerebral vascular disease was examined months after the acute illness which had left him aphasic. An attempt was made to have him believe that he was not being tested, and the conversation was limited to "small talk." At the end of the interview he said the Amytal made him feel better; his speech, however, was actually worse.

Patients who were particularly disturbed by their speech difficulty sometimes showed a "catastrophic reaction" when Amytal was given. One of these, previously an accomplished draftsman, became angry with himself and hostile toward the examiner. He began to cry, and it appeared that the Amytal had broken down some of the defenses he had set up against his disability. On one occasion he cried "Insult! Insult!" when he found himself unable to do a simple sum.

DISCUSSION

Linn and Stein[1] reported three cases of aphasia due to brain injury in which 0.5 gm. of sodium Amytal intravenously improved the patient's speech. In one case the improvement continued for two days after the injection. Linn[2] later described transient improvement of aphasia with Amytal administration in two additional cases. He suggested that the improvement was due to the removal by Amytal of the inhibiting effect of anxiety. As mentioned previously, those patients in our series who had considerable anxiety reacted particularly badly to the drug.

Billow[3] gave multiple injections of sodium Amytal to two patients with aphasia and hypertensive cerebrovascular disease. In one, progressive improvement of aphasia occurred and was maintained with each injection through the fourth. No further improvement resulted after two more injections. In the second case, improvement was noted with the first two injections, but four later attempts did not affect the aphasia.

Spontaneous fluctuations in performance occur in aphasic patients and, as was apparent in our study, these fluctuations may be accentuated by sodium Amytal. Performance of certain test items may improve under sodium Amytal, while at the same time performance of other items becomes poorer. Thus, if only the improvement is noted, a false impression may be gained concerning the overall change in the aphasia.

SUMMARY

1. Twenty-seven unselected patients with aphasia were studied in an attempt to determine the effect of intravenously administered sodium Amytal upon the language defect.

2. There was no real improvement in any patient during or after the administration of sodium Amytal. In some cases there was an apparent

increase in the patient's ability to speak or understand, but this increase was within the limits of the fluctuations which occurred spontaneously before the drug was administered.

3. Up to the point at which nystagmus appeared, small amounts of sodium Amytal had no effect on aphasia in these patients.

4. Larger amounts of sodium Amytal, sometimes carried to the point of drowsiness, usually made the aphasia worse.

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The subject of aphasia is of such interest, and so much attention has recently been given to it by physiologists and pathologists, that, although it is only a symptom common to several morbid conditions, a treatise on diseases of the nervous system would scarcely be regarded as complete without its being fully considered.

The fact that the faculty of speech may be deranged independently either of the will, paralysis, or loss of voice, appears to have been noticed at a very early period in the progress of science. Thus Isaiah says, "For with stammering lips and another tongue will he speak to this people;" and again, "Thou shall not see a fierce people, a people of a deeper speech than thou canst perceive; of a stammering tongue that thou canst not understand."

Thucydides mentions that many, who suffered from the plague which raged at Athens, found on recovering that they had not only forgotten the names of their friends and relations, but also their own names.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

Treatment Review

Neurologic Rehabilitation

Pearce Bailey, M.D.

The current rehabilitation movement, or the third phase of medicine, as it is termed by Rusk,[1] is rooted in the concept that the mission of modern medicine must extend beyond definitive medical treatment to a program of dynamic therapeutics designed to bring the chronically ill patient to the highest functional level of physical, psychological and socio-economic adjustment compatible with his disability. In order to prevent chronic invalidism, the physician broadens the scope of medical practice to include the application of active therapeutics during convalescence. His responsibility does not cease with bedside treatment, but follows the patient through a coordinated rehabilitation process, from bed to job, or to a life of self-care at home. He mobilizes all therapeutic influences, physical, psychological and socio-economic into a program of total care. Such a program requires a "team" approach wherein the physician and allied professional personnel unite to form a therapeutic unit. It also requires the acceptance, by the physician and other therapists, of limited therapeutic objectives.

The modern rehabilitation movement arose from the medical exigencies of World War II and was later implemented by the medical program of the Veterans Administration[2, 3] and by the statistical revelation of the ever increasing life span of the average American.[4]

Today most organized medical rehabilitation programs are confined to a few large medical centers and government hospitals. It is evident, however, that the movement is gaining momentum, and it seems logical to predict that it will extend widely into civilian practice.

APPLICATIONS TO NEUROLOGY

The principles of rehabilitation have a special application to disabilities in the neurologic field. Many neurologic disorders are peculiarly susceptible to rehabilitation for obvious reasons. To begin with, the pathogenesis of many neurologic disorders is not known; hence there is no specific therapy and any therapeutic goal must be limited to maximum development of residual functions. Also by virtue of their often crippling and unsightly nature, neurologic disorders may be accompanied by severe psychological and socio-

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economic frustrations. This requires retraining on several levels of adaptation: neurologic, social and vocational.

Therefore, it is not surprising to see how constructive some programs of neurologic rehabilitation can be when properly planned and executed. For example, Baker and Brown[5] have demonstrated that 75 per cent of a large group of bedridden neurologic patients in all categories, who had been hospitalized from three to 20 years, could be and were discharged to their homes in varying degrees or readjustment, ranging from gainful employment to a life of independent self-care at home.

Neurologic rehabilitation is applicable to a variety of neurologic conditions, including hemiplegias, paraplegias, multiple sclerosis, parkinsonism, poliomyelitis, cerebral palsies and certain epilepsies. It is well to remember, however, that certain neurologic disorders are not susceptible to rehabilitation.[6]

EARLY PHASES OF THE REHABILITATION PROCESS

Baker and Brown[5] have divided the beginnings of the nerologic rehabilitation process into three principal phases: 1) evaluation of the patient; 2) setting the therapeutic goal; and 3) organization of the therapeutic program.

Evaluation of the patient: Since the aim of the program in neurologic rehabilitation is to restore residual functions to maximum efficiency and develop new potentials in the physical, psychological and socio-economic status of the patient, it is essential that he be evaluated accurately in all these spheres of activity. There should be a complete general medical examination and, in addition, special study should be made of the patient's vascular tension, cardiac reserve and orthopedic status, inasmuch as the condition of the patient in relation to those factors is apt to be decisive in the ultimate therapeutic consequences.

A complete neurologic examination should be given, but its scope should be expanded beyond the routine examination given by clinical neurologists schooled in the traditional clinico-anatomical methodology. Not only should the extent of disordered structure and function be measured, but also an appraisal should be made as to the extent that residual functions or accessory neural mechanisms can be developed through retraining methods to substitute or compensate for lost functions.

The neurologic examination also should investigate the patient's mental and emotional state more thoroughly than is usually done in routine examinations. The disabled neurologic patient may suffer from reduced adaptive capacity due to brain damage; his emotional reaction to his disability may approach catastrophic proportions; and the entire clinical picture may be colored by his basic personality structure.[7] This triad of brain damage, reaction to disability, and basic personality structure constitutes a group of interacting forces which must be brought into clear diagnostic perspective before the therapeutic limits of the rehabilitation process can be determined.

Complementing the neurologic examination are the social and vocational evaluations of the patient. The former comprises a study of the economic and moral resources of the patient's home situation, his attitude toward his family and their attitude toward him, and the nature of his social setting. The purpose of a vocational evaluation is to measure the

patient's interest and aptitudes in order to predetermine his vocational and avocational limits. Both the social and vocational evaluations are essential factors for planning the therapeutic objectives and the final adjustment of the patient.

Setting the therapeutic goal: When the evaluation of the patient is complete, a therapeutic goal should be set which is compatible with his remaining physical assets, emotional reserve and socio-economic prospects. The goal of achievement naturally varies widely from patient to patient. Care should be taken not to set the therapeutic goal at too high a level of performance, especially for patients suffering from organic brain damage, for they are prone to regress if the goal is beyond their residual capacities.

Organization of therapeutic program: The third and last phase of the rehabilitation process is the initiation of a therapeutic program which is compatible with the patient's physical status and his predicated level of achievement as determined by the therapeutic goal. Such a project requires: 1) organization of a therapeutic team; 2) prompt initiation of therapeutic procedures; and 3) continuous application of therapeutic procedures.

In a hospital, the therapeutic team ordinarily consists of a physician in charge, personnel in the field of physical medicine and rehabilitation, as well as trained personnel in nursing, psychology, social service and speech therapy. The various members of the team should be harmoniously integrated into a functional unit which combines medical and socio-economic therapeutics in the treatment program. Periodic neurologic conferences, in which all members of the therapeutic team participate, serve to implement the integrative action of the therapeutic team. At these conferences a complete survey of the patient's physical, psychological and social status is presented in order to orient the rehabilitation team in the implications of the diagnosis, the prescribed therapeutic goal, and the patient's potentialities for resocialization and reemployment. If properly conducted, these conferences automatically create an atmosphere of group motivation, which is an essential element for optimum results in the rehabilitation of disabled neurologic patients.

Once a competent therapeutic team has been formed, treatment should be instituted early. The purpose of early treatment is to avoid the known deconditioning effects of prolonged activity on biologic economy.[9, 10] When it is once initiated, the therapeutic program should be allowed to continue without break or interruption, such as might be occasioned by the transfer of a patient from one hospital service to another for the management of different phases of the rehabilitation process. Such interruption of treatment makes it difficult to follow the overall progress of the patient and reduces group motivation. Therefore in a hospital program, neurologic rehabilitation should be an integral part of, or closely associated with, a neurology service.

EARLY TREATMENT PROCEDURES

Treatment during the acute phases of neurologic disability is more or less routine and needs no special comment here. As the acute stage of neurologic disability merges into the subacute stage, the initial procedures of the rehabilitation process are begun. These procedures include bedside physical therapy to correct bed posture, maintain body alignment and prevent contractures, as well as planned measures

for the control of pain, decubiti, sphincteric disturbances and mental and emotional disorders. Detailed descriptions of these procedures may be obtained from standard articles and texts.[5, 8, 11, 12] Speech and language retraining for dysarthric and aphasic patients often may be begun at the bedside.

When the patient has successfully passed through the acute and subacute stages of neurologic disability, he is ready to switch his role from that of a passive recipient of care to that of an active participant in the rehabilitation process. At this point he is gradually guided into the stage of active retraining. The pricipal procedures employed during this stage concern: 1) physical therapy; 2) the application of orthopedic appliances, if indicated; 3) retraining in self-care and ambulation; and 4) social therapy.

PHYSICAL THERAPY

As soon as the patient's condition permits, he is brought to the physical therapy unit where the massage used at the bedside may be supplanted by local immersion baths, such as the whirlpool bath[13] which exerts a sedative effect, relieving pain and muscle spasm and permitting the movement of weak or painful extremities with greater ease.

Stripped of its instrumentations and technicalities, physical therapy as applied to disabled neurologic patients consists of heat, massage and exercise. As a general rule, some form of heating should precede massage or exercises. Such a preliminary warming renders structures more supple and relaxed for manipulation or active exercise. For general purposes, infrared radiation is an efficient form of heating. However, diathermy is sometimes used, particularly in conditions in which the acute etiological factor is no longer operating. Descriptions of the clinical uses of various forms of heat therapy can be found in standard texts on physical medicine.[14, 15]

During the early phase of active retraining, mobilization of joints is continued at the bedside. In addition, full range of motion activities for all body joints as well as passive and active underwater exercises can be begun in specially constructed tanks, such as the Hubbard tank. The buoyancy of water permits certain exercises otherwise not possible. Therapeutic tanks combine the effects of heat and mechanical massage and are of particular value for spastic and flaccid paralysis, muscular incoordination, and neurologic conditions which require metabolic and psychologic stimulation.

The early establishment of a well-planned exercise program is essential to the rehabilitation process.[5, 16] The purpose of an exercise program is to build power in weakened muscles and relax antagonists; to restore muscle function to the limit by substitution devices and special retraining technics (neuromuscular reeducation); and to provide an effective method for the restoration of general physical fitness and for the release of emotional tension.[16]

The usual procedure for disabled neurologic patients is to graduate them through various functional levels of exercise activity, namely, passive, active assistive and active.[5, 16] Common forms of therapeutic exercises used with neurological patients are pulley therapy, muscle setting, resistive exercises, and ataxia exercises.[5, 16] In addition to exercises designed to reestablish maximum function, there should be included reconditioning ex-

ercises or calisthenics to enable the patient to recover strength lost by inactivity, augment general physical fitness and reduce emotional tension.

Since the success of the exercise program depends largely upon the amount of effort put forth by the patient, it is imperative to maintain performance in line with the patient's potential. This requires in addition to technical skill, a high degree of individual and group motivation. A practical method to provide such motivation is to have the exercise room in close proximity to the neurology ward, where patient activity and progress is under the constant observation of the neurologic staff. The equipment of the exercise room should be of simple construction in order that it may be duplicated in the home where many patients can complete the final phase of the rehabilitation process.

ORTHOPEDIC APPLIANCES

Knowledge of conservative orthopedic methods is important in neurologic rehabilitation. Properly constructed and fitted appliances are useful to avoid skeletal deformities, to diminish pain and muscle spasm, to prevent a deformity from becoming fixed, and to improve skeletal function. Common appliances used with neurologic patients are casts, splints, traction devices and braces.

It is important that members of the therapeutic team understand the basic principles underlying orthopedic devices, in order that they may instruct the brace maker regarding the construction of desired appliances. It should be remembered, however, that bracing is used primarily as a means to an end. It is not to be employed as a substitute for functional capacity which might be developed through the neuromuscular training of the limbs being braced.

SELF-CARE AND AMBULATION

Neurologic disorders usually result in a greater loss of ability to care for one's daily needs than other comparable disabilities. This often robs the patient of self-esteem, burdens attending hospital personnel, and increases the cost of care of the patient. Consequently, all members of the therapeutic team should contribute to the self-care and ambulation program and be conversant with the status of each patient in these activities at any given time. Self-care activities are best taught by the direct use of the patient's personal effects and facilities.

Ambulation exercises start with balancing in parallel bars, followed by training in the principles of crutch and cane gaits, and finally unassisted walking. A patient may start at any stage, depending on his condition at the time of referral and his ability to learn. Before discharge from the hospital the patient should be trained to cross streets, climb curbs, ascend and descend stairs, street car and bus steps, walk to his meals and the lavatory, and get along with his wheel chair. A section of the exercise room (50 feet long) should be set aside for ambulation exercises and modelled according to tested specifications.[5]

SOCIAL THERAPY

The ultimate objective in neurologic rehabilitation is the resocialization of the patient and his proper adjustment in a suitable occupation or at home. In the acute and subacute stages of disability the nurse is in a strategic position to establish rapport with the patient and his relatives, and thus initiate the resocialization process. Similarly, the physical therapist makes an

early contact with the neurologic patient and is in a strategic position to reorient the patient, particularly on an emotional level. A competent physical therapist is able to detect early emotional disturbances, resolve the simpler problems, and apprise the physician of the more complicated ones.

The corrective therapist, by participating in both individual and group retraining exercises, plays a dominant role in the resocialization process from the time the patient leaves his bed until his discharge from the hospital. However, it is in the development of group exercise activities, under conditions of controlled competition, that the corrective therapist makes his greatest contribution to the resocialization of neurologic patients. Group exercises should be interspersed with recreational or game periods which break monotony and often generate an enthusiasm which is carried back to the exercise program.

As the patient progresses he undertakes activities in occupational therapy which bridges the gap between medical and social therapeutics, for it operates in both spheres and tends to join them.[17] It is used to hasten physical well being and motivation and to provide the proper social and vocational direction in the rehabilitation process. In general, it has been found that weaving in its various forms provides the most adaptable medium for neurologic patients.[5]

An important figure throughout the total rehabilitation process is the social worker. The task of the social worker is to evaluate the patient's social setting, his work record and his economic status. This information is most essential for determining the therapeutic goal and for coordinating medical and socio-economic activities. As the patient's adjustment progresses, the social worker attempts to enlist cooperation from the patient's family and induce them to participate in the overall rehabilitation program. The social worker's final task, in collaboration with the vocational advisor, is to open avenues to job placement.

In neurologic rehabilitation the activities of the physician in charge are not confined to strictly medical procedures. He contributes to the resocialization process by functioning as coordinator of the therapeutic team. He apportions social therapeutics in accordance with the individual medical needs of each patient. He schedules both medical and social activities to avoid conflict and, at the same time, to give the patient as full a day as is compatible with his neurologic status. Finally, it is his responsibility to maintain morale among the therapists and keep them functioning, not as a mere aggregate of individuals but as a harmoniously integrated unit.

ROLE OF THE NEUROLOGIST

The development of neurologic rehabilitation offers a unique opportunity for the neurologist to expand the scope of his activities into a specialized field of therapeutics. In a hospital program the neurologist with some training in the principles and practice of rehabilitation is equipped to serve ideally as the physician in charge of a program of neurologic rehabilitation. Or, he may serve in such a program as a consultant to the physiatrist, who has had training in neurology. In either role, however, for optimum results it is imperative that the neurologist function not merely as a diagnostician but as a true physician dedicated to follow the patient from bed to job or to an adjustment at

home. That there may be a trend in this direction is evidenced by the fact that some residency training programs in neurology now provide for rotation through services of physical medicine and rehabilitation.

Hospital programs, however, can act only as springboards for the wider use of neurologic rehabilitation procedures in general practice. Many rehabilitation activities for the milder types of disability or for the end phases of the more serious forms may be performed at low cost in the home. Essential equipment is simple and inexpensive to construct. Cooperative members of the family can be trained to function as a therapeutic team. Here again the neurologist versed in rehabilitation may serve as the physician in charge, or as consultant to the general practitioner upon whose shoulders the bulk of the rehabilitation problem must eventually fall.

SUMMARY

The philosophy, principles and historical background of the modern rehabilitation movement are stated. Its special application to the field of neurology is discussed. The early phases of the rehabilitation process are described. Essential treatment procedures, including physical therapy, the use of orthopedic appliances, retraining in self-care and ambulation, and social therapy are delineated briefly. The role of the neurologist in the rehabilitation movement as a means to expand the scope of his activities into this specialized field of therapeutics is considered.

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Neurology

Clinical Pathological Conference

From the Division of Neurology and Neurological Surgery
and the Laboratory of Neuropathology,
University of Kansas School of Medicine

Presented by
A. Theodore Steegmann, M.D. and William P. Williamson, M.D.

PRESENTATION OF CASE

A 35 year old white male farmer was brought to the emergency room in a comatose condition at 11:00 p.m. on February 1, 1950. His wife stated that he became ill two weeks before and complained of headache, loss of appetite and fatigue. He soon began to have nausea and vomiting. Since childhood his left ear had periodically discharged foul-smelling pus following headache and fever. His present illness had started in a similar fashion. One week before coming to the hospital he experienced difficulty in finding words to express himself and had a tendency to perseverate. His wife also noticed some dragging of his right leg in walking. He was given penicillin by his family physician but continued to grow worse and on the evening of admission he had a short tonic convulsion with twitching of the right side of his face. This was followed by stupor.

Examination in the emergency room revealed a well developed, acutely ill, stuporous man. His temperature was 104° F., respirations were 24 per minute, pulse 48 per minute and blood pressure 220/80 mm. Hg. There was a foul purulent drainage from the left ear. The right pupil was small, the left dilated, and the light reflex was absent. Both optic discs showed a mild papilledema. The deep reflexes were universally hyperactive and Babinski's sign was present on both sides.

DISCUSSION

DR. STEEGMANN: The problem of diagnosis presented by an unconscious patient brought into the emergency room was simplified by the history obtained from the wife. A history of chronic otitis media on the left side with periodic exacerbations immediately suggests an intracranial spread of infection. The development within a week of language difficulty, focal convulsive seizure with twitching of the right side of the face, dragging of the right leg in walking and stupor would point to the left temporal region as the probable site of spread. When this is correlated with the clinical observations, namely fever, slow pulse, dilated left pupil, papilledema and bilateral

Babinski sign, an abscess in the left temporal lobe would be the most logical clinical diagnosis. The possibility of an extradural abscess or a localized non-suppurative encephalitis in the same general region could not be excluded without surgical exploration. Since the patient was desperately ill, an immediate craniotomy was indicated.

CASE HISTORY *(continued)*

The patient was sent immediately to the neurosurgical operating room, and under local anesthesia a trephine opening was made over the left temporal lobe. A needle introduced about one centimeter into the temporal lobe encountered an abscess, and about 20 cubic centimeters of foul smelling pus was aspirated. A rubber drain was introduced into the area and the wound closed. The left pupil returned to the size of the right pupil and the patient was more responsive the following day.

Laboratory examination the morning after admission revealed a red blood cell count of 4,920,000 per cubic millimeter; hemoglobin 13 grams (84 per cent); white blood cell count of 11,900 per cubic millimeter with polymorphonuclears 75 per cent, filamented 75 per cent, lymphocytes 18 per cent and eosinophiles 4 per cent.

The patient was treated vigorously systemically with penicillin, Streptomycin and sodium sulfadiazine, and the abscess cavity was irrigated daily with 100,000 units of penicillin. He remained stuporous and the initial improvement did not continue but the pulse rate elevated to 72 per minute after the second post-operative day. Aureomycin was given without benefit. His temperature after the first few days fluctuated between 101° F. and 104° F.

DISCUSSION *(continued)*

DR. WILLIAMSON: The patient's critical condition on admission demanded immediate relief of increased intracranial pressure with the least possible surgical trauma. The patient was not believed to be in condition to tolerate ventriculography, radical craniotomy and total excision of the abscess, which is ordinarily preferable to simple drainage. For this reason simple needling on the basis of clinical localization was done and the abscess cavity was successfully located and drained. It was hoped that the patient's condition would improve enough to carry out further surgery electively, or that chemotherapy directed both parenterally and into the abscess cavity would bring about recovery without further surgery. However, by the seventh postoperative day it was apparent that neither had occurred, and it seemed essential to establish further whether the initial abscess had refilled or whether multiple abscesses existed.

CASE HISTORY *(continued)*

A ventriculogram made February 9, 1950 showed displacement of the ventricular system to the right, with displacement upward of the left anterior horn and mid portion of the left ventricle. The left posterior horn did not visualize. It was concluded that abcess formation had recurred or had been evacuated incompletely. A subtemporal craniectomy was carried out and a poorly loculated abscess extending posteriorly and inferiorly in the temporal lobe was exposed. The capsule was not well enough organized to shell out in toto, so the abscess cavity was evacuated completely under direct vision. An indwelling catheter for penicillin instillation and additional drains were inserted and the wound was closed. The previously instituted therapy plus Aureomycin was continued. Cultures of material from both operations were taken. An anerobic organism was isolated but the bacteriological laboratory was never able to identify it with certainty. No organisms were isolated in blood cultures.

Postoperatively the patient was improved but was considered an aphasic. His temperature continued to fluctuate between 101° F. and 104° F. with a tendency to lysis. Aureomycin was discontinued on February 15, 1950 with a recurrence of septic spiking of temperature. Another ventriculogram made on February 19, 1950 revealed no ventricular distortion. The ventricular fluid contained only 8 cells per cubic millimeter.

DISCUSSION *(continued)*

DR. WILLIAMSON: Ten days had elapsed after radical abscess drainage, yet the septic course and poor condition of the patient continued. It was felt necessary to investigate the status of the abscess and to determine whether a meningitis was present. The ventriculogram excluded abscess and the cell count of the cerebrospinal fluid eliminated a meningitis. It appeared that the mastoiditis must account for the lack of improvement, and the patient was transferred to the otolaryngology department.

CASE HISTORY *(continued)*

The otolaryngology department had previously recommended mastoidectomy following recovery from intracranial surgery. A left radical mastoidectomy was performed on February 20, 1950. Foul smelling yellowish green pus was found in the mastoid cavity. Large areas of cholesteatomatous material filled the cavity. A small fistulous tract communicated with the horizontal semicircular canal. Exposure of the dura revealed no evidence of increased intracranial pressure, and there was no necrotic tissue overlying the lateral sinus. Cultures of mastoid tissue demonstrated proteus vulgaris and staphlococcus aureus.

Following surgery the patient improved temporarily but he continued to run a temperature between 102° F. and 104.5°F. On February 24, 1950 a spinal puncture was done. The cerebrospinal fluid was under a pressure of 154 mm. of water. The fluid contained 9 leucocytes per cubic millimeter, and a total protein of 34.5 mg. per 100 ml. Jugular compression on the right produced a rapid rise of pressure to 278 mm. of cerebrospinal fluid and an equally rapid fall to the initial pressure. Compression of the left jugular gave no response.

These observations pointed to a left lateral sinus thrombosis. The left lateral sinus was explored on February 24, 1950. An extensive organized thrombus was present. It extended inferiorly to the jugular bulb and into all of the lateral sinus exposed at operation. The jugular vein was not ligated, and dicumerol therapy was started without improvement. The patient remained in a septic condition and ligation of the jugular vein was considered. On February 28, 1950 the lateral sinus was again explored and the thrombus was found to extend inferior to the jugular bulb. Ligation was rejected. The patient showed a progressive downhill course. He developed diffuse rales in his chest and died March 4, 1950.

DISCUSSION *(continued)*

DR. STEEGMANN: After a long stormy illness, the patient finally died, not as a result of the brain abscess which apparently healed after radical drainage, but as a result of another complication of the mastoid infection. It appeared certain before death that a pulmonary conplication had taken place. The danger of pulmonary embolism had been considered. Jugular ligation with the use of anticoagulants, preferably heparin, should have been tried.

AUTOPSY

DR. STEEGMANN: The only important pathologic observations, exclusive of the head, were multiple areas of infarction at the bases of both lungs, more extensive on the right. A pulmonary embolus was found in the main pulmonary artery, extending into its inferior branches. The infarcted areas in the lungs were of different stages of development histo-

FIG. 1. Horizontal section through left inferior temporal region to show area of cavitation and softening.

logically. Some of the thrombi in the larger pulmonary arteries were undergoing early organization. Pulmonary edema, atelectasis and cardiac dilatation were present.

The skull showed bony defect from the craniectomy and mastoidectomy. The brain in situ exhibited a healed horizontal incision into the left temporal lobe 4 cm. in length, lying 4 cm. above the inferior temporal surface. The base of the skull contained a necrotic area in the left temporal bone 1 cm. in diameter, lying in the superior posterior aspect of the left petrous process, 3 cm. from the temporal portion of the calvarium. The dura mater overlying this area was densely adherent. There was a fixed adherent ante-mortem clot lying in the lateral sinus, throughout the extent of the lateral sinus, and extending down into the internal jugular vein.

Histologically the temporal bone in the mastoid area contained necrotic spicules. The connective tissue constituents were infiltrated with mononuclear cells, lymphocytes and polymorphonuclear leucocytes. There were many macrophages, some containing refractile greenish brown pigment. Several multinucleated giant cells of the foreign body type, fibroblasts and proliferated capillaries were present. Epithelial-lined cystic spaces were visible in several bony lacunae. The organized thrombus in the lateral sinus was partially recanalized. The organizing thrombus contained the same type of cells described above in the mastoid bone. In one area within the thrombus, giant cells surrounding wavy strands of tissue resembling cornified epithelium were seen.

The formalin fixed brain weighed 1140 gm. Its external appearance with the exception of the left temporal lobe was normal. The left middle and inferior temporal convolutions were soft to palpation, and the area of surgical incision was superficially healed. Section of the brain stem, cerebellum and brain, exclusive of the left temporal lobe, revealed no gross pathologic changes except prominent vascular points. Horizontal sections through the brain revealed no ventricular dilatation. There was an area of subcortical softening in the left temporal lobe underlying the superior, middle and inferior temporal convolutions, being

more extensive in the posterior region. Its greatest diameter was in the inferior temporal convolution in a zone corresponding to the level of the posterior one-third of the thalamus, at which area it measured 3.5 cm. by 1.5 cm. in diameter (figure 1). The softened tissue was granular in appearance and light brown in color. It extended through the base of the temporal lobe in one small area.

The histologic changes in the brain and meninges deserve description. A section of dura mater shows a patchy infiltration of lymphocytes, polymorphonuclear leucocytes, and macrophages lying in loose proliferated connective tissue. One vein, the lumen of which contained an organizing thrombus, had a small abscess in its wall. The larger branches of the left middle cerebral artery were not thrombosed.

No focal lesions were present in the brain stem, cerebellum or brain, apart from the left temporal area. In the left temporal area there was a light hyperplasia of the leptomeninges with mild infiltration of lymphocytes, endothelial cells and macrophages. Many of the small arteries exhibited endothelial swelling and proliferation. (obliterating arteritis). The subcortical softening consisted of necrotic tissue near the area of cavitation with an abundance of debris and gitter cells in the marginal zone. The wall of the softening contained many lymphocytes and plasma cells but polymorphonuclear leucocytes were seen rarely. Lymphocytic infiltration was present around many of the blood vessels. Around others these were collars of gitter cells. A light mesenchymal and vascularized stroma containing reticulum fibers was growing into the necrotic zone. The degenerated zone was demyelinated. One area of hemorrhage was seen in the necrotic area. Lying adjacent to the cortex was a zone of glial cell proliferation, especially protoplasmic astrocytes, in clumps and diffusely proliferated. The ganglion cells of the cortex were injured. Shrinkage, chromatolysis and severe cell disease were present. Occasional refractile crystals (?penicillin) and giant cells were present in the area of cavitation.

Two small focal areas of softening without cavitation were observed. One was medial to the knee of the left internal capsule, the other lateral to the internal capsule, adjacent to the globus pallidus. These were presumed to be the result of injury to small arteries traversing the edge of the inflammatory zone which extended deep medially in the temporal lobe (? branches anterior chorioidal artery).

A vertical section through the base of the temporal lobe, at the point where the lesion extended through the cortex, revealed destruction of the cortex lying along the edge of a sulcus on both sides. The widened sulcus showed proliferated meninges infiltrated with lymphocytes, plasma cells and macrophages. Occasional small veins filled with an early organizing thrombus were seen. Small arteries in the same area exhibit proliferative occluding arteritis. The cortex along the sulcus was entirely destroyed by encephalomalacia.

CONCLUDING DISCUSSION

DR. STEEGMANN: It is probable, in this case, that infection in the mastoid area had spread to the temporal lobe by more than one route. The presence of chronic necrotizing mastoiditis with necrosis of the petrous portion of the temporal bone, accompanied by thickening and adhesions of the overlying dura, indicate contiguous direct extension upward. Lateral sinus thrombosis

with evidence of intramural abscess of dural veins suggest retrograde spread along venous channels. The operative note indicates that the mastoid infection had also spread into the horizontal semicircular canal. The abscess cavitation in the temporal lobe was probably facilitated by occlusive vascular factors, both arterial and venous. The absence of the classical histologic picture of a healing brain abscess can probably be explained by the local and systemic effect of antibiotic medication. In fact, our concept of the histologic appearance of a brain abscess may have to be altered, now that the antibiotic drugs are in common use. Cholesteatoma could not be proved because surgical specimen of the mastoidectomy material was not obtained. It was suggested by the presence of giant cells and cornified epithelium in the temporal bone and lateral sinus thrombus, but giant cells were also present in the temporal lobe cavity and may have been stimulated by penicillin crystals.

It is unfortunate that the patient's life was not saved after surviving successful treatment of his brain abscess. He would probably have been an aphasic, considering the size of the subcortical temporal lobe lesion. His death was unquestionably the result of pulmonary embolism, secondary to lateral sinus thrombosis. It is possible that ligation of the left internal jugular vein and the active use of heparin might have prevented the terminal complication. The problems of therapy presented by this patient were difficult from the start.

The encephalic nerves have certain peculiarities of origin and of exit which we may have further occasion to mention in connection with the forms of injury to which these trunks are liable.

The spinal nerves arise from either side of the medulla by two roots, distinguished as anterior and posterior, each having a number of rootlets. Those which form the posterior root pass through a small ganglionic enlargement; those of the anterior stem units without passing into a ganglion; and both sets of fibres on coming together constitute one spinal nerve. The anterior root is motor in function; the posterior, sensory: the former carries messages from, and the latter to, the nerve centres. Thus constituted, the compound nerve passes outward until its fibres, separating anew into their physiological constituents, enter the muscles on the one part, or are distributed to the surfaces upon the other.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Neurology

.....BOOK REVIEWS....

Electroencephalography in Clinical Practice

Robert S. Schwab, M.D. 1951. Philadelphia: W. B. Saunders Company, 195 pages, $6.50.

The stated purpose of this book is to discuss the uses and limitations of electroencephalography in the diagnosis and study of diseases of the nervous system, not to provide a manual for the electroencephalographer. It is directed to neurologists, internists, psychiatrists and neurosurgeons to the end that electroencephalography may be intelligently combined and correlated with all other diagnostic procedures in these fields and so reach the full measure of helpfulness.

Following an historical summary, the author discusses the relation of electrophysiology and anatomy to electroencephalography. The normal electroencephalogram in childhood, adolescence and in the adult state is described. The chapter on technique is concise and, within the framework of the plan of the book, comprehensive. Divergent viewpoints on methods are described and a controversial attitude is avoided. The electroencephalogram in epilepsy and in other neurologic and neurosurgical problems is presented quite adequately. The use of electroencephalography in psychiatry may prove illuminating to many readers; it is recalled that Hans Berger, the first clinician to use electroencephalography, was a psychiatrist and that a large measure of encouragement and support for the method has come from psychiatrists. A discussion of laboratory organization, training of staff and interpretation of records will be of value to hospital administrators, and the discussion of the electroencephanogram in research will suggest to workers in other fields the inclusion of contributions in electroencephalography as a source of fruitful applications to their own investigations. The book contains a glossary and is satisfactorily indexed.

There is a very real place for this volume. It is ideally suited to interns and residents who, having become interested in electroencephalography, request something that may give them more information and detail. Opinion may differ as to whether it is sufficiently detailed and comprehensive to satisfy adequately the expectations of neurologists, psychiatrists and neurosurgeons. It is the reviewer's belief that the book will be a means of creating interest in electroencephalography and will give impetus and encouragement to its further progress.

A. R. V.

The 1950 Year Book of Neurology, Psychiatry and Neurosurgery

Edited by Roland P. Mackay, M.D. (Neurology), *Nolan D. C. Lewis, M.D.* (Psychiatry), *and Percival Bailey, M.D.* (Neurosurgery). *1951. Chicago: The Year Book Publishers, Inc., 627 pages, $5.00.*

Each of the three sections of *The 1950 Year Book of Neurology, Psychiatry and Neurosurgery* is prefaced by a review of the progress made in the specialty during the decade 1940-1950.

Dr. Mackay, reviewing neurology, stresses the contributions resulting from the study of cortical disease, electrostimulation both at the operating table and in the laboratory, and neuronography by strychninization. He mentions the work of Magoun and others which shows that the diencephalon and brain stem exercise facilitatory and repressor influences over the cortex, and that of Snider which demonstrates that the cerebellar cortex receives exteroceptive as well as proprioceptive impulses. Under his discussion of frontal lobotomy he states that the procedure "deprives the subject of much emotional intensity and color and of much intellectual vigor and capacity for self criticism. There is, however, growing doubt as to how permanent such deprivation is." In his review of diagnostic methods, Mackay evaluates electroencephalography, angiography, electromyography and the use of radioisotopes. He concludes his review by stating that the most significant movement in the treatment of neurologic patients during the past decade has been the increasing stress on rehabilitation.

Dr. Bailey reviews the history of the development of neurosurgery. He states, "By 1940 the diagnosis of brain tumors had been facilitated not only by the increasing knowledge of cerebral physiology and clinical neurology but also by roentgenology, ventriculography, arteriography and that of spinal tumors by myelography. In the last decade little has been added to our resources by roentgenology or ventriculography, but arteriography has increased its usefulness by the invention of percutaneous puncture and its extension to the vertebral arteries. New radiopaque substances have been created." He mentions the advances that have been made in electroencephalographic localization, in the treatment of infections, in the control of hemorrhage, and in the treatment of hydrocephalus. Among the most important developments of the past decade he cites the increase in operations whose purpose is in some way to alter the function of nervous tissue, especially the brain. Among these are psychosurgery, treatment of epilepsy, and attempts to relieve spasticity, rigidity, tremor and athetosis.

Dr. Lewis, too, presents an excellent critical review. He makes a plea for more exhaustive studies for brain changes in psychotic patients, further chemical studies to investigate metabolic disorders as the basis for mental diseases, and further study of spectromicroscopic and electron microscopic changes in the nerve cells as a possible basis for alterations in the behavior of animals and man.

As has been the case in the past, the *Year Book* presents to the reader a critical appraisal of the work that has been done in the three specialties during the past year.

R. N. DeJ.

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NEWSLETTER

NOVEMBER-DECEMBER, 1951

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AMERICAN ACADEMY OF NEUROLOGY

Macdonald Critchley Gives Impressions of American Neurology

Following his recent visit to this country, Macdonald Critchley, dean of the National Hospital, Queen Square, London, jotted down some of his impressions of neurology in general and of American neurology in particular. He writes: "One wearies of being told that the study of nervous disease is without future; that the neurological clinician is moribund; and in particular that the medical neurologist is in poor shape. But one's experience in North America does nothing to support these contentions. On the contrary. The impression remains that, whatever the difficulties which have in late years beset our specialty, the present outlook is most gratifying. Neurology today is as promising a field of medical endeavour as it ever has been. Having encountered in America neurophysiologists who are philosophers at heart; neuroanatomists of wide culture and vision; clinicians who are as disciplined as any experimentalists; and neuropsychiatrists who are also scientists, one can look forward with confidence to a time of ripe achievement.... The neurologist who aspires to achieve clinical mastery need defer to no one. It is necessary however for him to maintain the integrity of his art and of his teaching. Short cuts are out of place. There are times, and this is becoming an international fault in no way to be laid at the doors of American authors, when the literature has been accepted, taken as read, up to the time of the latest contribution. This is dangerous as well as improper. The bibliography should always be scrutinized with meticulous care. What you have to say has probably been said years before, perhaps many times before, and almost certainly in more graceful prose. To overlook an earlier reference is a solecism; to misquote or to misspell a byegone author is a faux pas which should carry the risk of social ostracism. All of us have erred in this way but it is time that we became alive to this growing impropriety; and if we are too old to cure ourselves we can at least indoctrinate our pupils....This is not a plea for an orientation towards the past, but for a golden mean. As Bacon said: 'There are found some minds given to an extreme love and appetite for novelty; but few so duly tempered that they can hold the mean, neither carping at what has been well laid down by the ancients, nor despising what is well introduced by the moderns'....Perhaps there may be an opportunity for British and American neurologists to meet again in combined session, as they did twenty-three years ago in London. Such an occasion would afford immense pleasure to all of us in Great Britain. Surely no diplomats are quite as successful as medical men."

International Congress of Neuropathology to be Held in Rome The First International Congress of Neuropathology will meet in Rome Sept. 8-13, 1952. Dr. Mario Gozzano, professor of neurology and psychiatry at the University of Rome, is president of the congress, while Dr. Armando Ferraro of New York serves as secretary general. Elected as honorary presidents of the congress are Professors U. Cerletti (Italy), J. G. Greenfield (United Kingdom), J. B. Hassin (U.S.A.), J. Lhermitte (France), O. Vogt (Germany)....The meeting, which is to last for six days, will include programs on the pathology of demyelinating diseases, vascular diseases, schizophrenia, mental deficiencies and senility. Neuropathologists, neurologists, psychiatrists and pathologists are cordially invited. The registration fee for active membership in the congress is $15.00. Further details may be abtained from Dr. J. H. Globus, Chairman, U. S. National Committee, 960 Park Avenue, New York City.

Panel of Neurologists Established A panel of international corresponding neurologists has been established at the National Multiple Sclerosis Society, 270 Park Avenue, New York City, according to C. H. Traeger, medical director of the society and founder of the panel. The panel comprises 56 neurologists from 26 countries, including Europe, Africa, South America, Australia and Mexico. The purpose of the panel is to serve as a clearing house for all information dealing with research in demyelinating diseases and to establish a liaison throughout the world with physicians and scientists interested in these problems....The NMS also has established a liaison with the Medical Sciences Information Exchange of the National Research Council, Washington 25, D.C., to assist in gathering information on all research in MS and demyelinating diseases pursued in the U. S....

Moore Comments on South American Trip Matthew T. Moore gave a series of lectures on transorbital lobotomy and abdominal epilepsy before the neurologic institutes of Brazil August 28-31. Commenting on his trip, Dr. Moore reports having received a warm and gracious reception from South American colleagues and described their work in neurology as being of high order. He makes special mention of the ingenious method for removing hydatid cysts of the brain developed by Professor Alejandro Schroeder and Dr. Arana of Montevideo; of the work of Prof. J. Alves Garcia of Rio de Janeiro on the secretory function and action of the hypothalamus; and of the interesting experimental work being pursued by Deolindo Couto, professor of neurology and director of the Neurological Institute in Rio de Janeiro. Dr. Moore also points to the pathological collection of Marchiafava-Bignami's disease, the world's largest, of Dr. Jacinto C. Orlando of Buenos Aires, and to the fine collection of brain tuberculomas and cysticercosis of Dr. Estaban Rocca, Oscar Trelles and Jorge Voto Bernales....Dr. Moore remarks, and rightly so, on the need of a closer liaison of Academy members with their South American colleagues.

* * * * * *

American Academy for Cerebral Palsy to Hold Annual Meeting in Boston M. A. Perlstein, secretary, announces that the American Academy for Cerebral Palsy will hold its annual meeting at the Copley Plaza Hotel in Boston, Friday and Saturday, November 16-17. All physicians interested in cerebral palsy are invited to attend the Friday afternoon scientific session. This session will present a dynamic program, listing such authorities as Bronson Crothers, Frances Hellebrandt, Morton Marks, William Cooper, Franc Ingraham and Wilder Penfield.

NINDB Program Now Under Way Dr. W. H. Sebrell, Jr., director of the National Institutes of Health, Public Health Service, has announced that the operating program of the recently established National Institute of Neurological Diseases and Blindness is well under way....For the fiscal year 1952 a total of $1,102,400 has been made available for research grants, fellowships and training grants to non-federal institutions.... The development of an internal research program, said Dr. Sebrell, has awaited the appointment of a well qualified staff for the new institute. Research planning has been initiated with the recent appointment of Dr. Pearce Bailey as director of the National Institute of Neurological Diseases and Blindness and with the appointment of Dr. Seymour S. Kety as scientific director....Commenting upon the future development of the new institute, Dr. Sebrell said: "We can expect both the research grant program and the internal research program to broaden considerably. In coordination with the professional societies and voluntary organizations, who both directly and indirectly have done much to make the new institute possible, we can expect to quicken our understanding of the many neurological disorders and thereby bring relief to thousands of sufferers."....It will be remembered that Dr. Sebrell addressed the AAN second biennial meeting held at Virginia Beach, April 11-13.

* * * * * *

Dr. Robert Bing Impressed by NEUROLOGY Professor Robert Bing of Basel, Switzerland, has written R. Wartenberg as follows: "Your new journal NEUROLOGY is a convincing testimony of the supremacy of the clinical methods in the vast field of our science and (as all real progress in medicine stems from the bedside) it will conquer and maintain a leading position amidst the other neurological journals."

Briefs Raymond D. Adams has been appointed associate clinical professor of neurology and chief of the neurological service at the Massachusetts General Hospital, succeeding Charles S. Kubik in both positions. Dr. Kubik is now lecturer in neuropathology and will continue his neurological research and practice at MGH....L. M. Eaton, consultant in neurology at Mayo Clinic, lectured on myasthenia gravis and neuromuscular disorders at the opening sessions of the three-day Postgraduate Medical Assembly of South Texas (July 23, 1951)....The American Board of Psychiatry and Neurology will hold its annual meeting and examinations at the Neurological Institute and the New York

Psychiatric Institute on December 17 and 18....The VA motion pictures, "Seizure-The Medical Treatment and Social Problem of Epilepsy" and "Introduction to Aphasia," were awarded first prizes at the Twelfth International Exhibit of Cinematographic Art held in Venice, Italy (August 8-18, 1951). Applications to obtain these films on a loan basis should be addressed to VA Central Office Film Library, Motion Picture Service, Department of Agriculture, Washington 25, D. C....T. L. L. Soniat announces a vacancy for a neurologist on the staff of the Ochsner Clinic, New Orleans 15, La....The Southern and Eastern EEG Societies met jointly at the Georgetown University Medical School (October 20-21).....Clark H. Millikan gave an address on "Sciatica" at the International Medical Assembly in St. Louis (October 23)....The EEG activities at the University of Illinois have been transferred from the department of psychiatry to that of neurology, Frederic A. Gibbs being named as professor of neurology....Among the 1951 winners of the American Public Health Association's annual Lasker awards were William G. Lennox and Frederic A. Gibbs, who were cited jointly as "able and effective investigators in epilepsy, whose work has saved a host of sufferers from misery." ...Members wishing to participate in the scientific program of the next Academy meeting, April 24-26, 1952, are reminded that the deadline for titles and abstracts is set for the first of November.

Paul Bailey

Complete Epileptic Seizure-control; First Step in Rehabilitation

In the drug therapy of the epileptic, nothing short of *complete* suppression of seizures can rightly be called full success. Complete seizure-control is a prerequisite to the patient's return to a normally active life. Carter[1] states: "Basically all efforts should be directed toward preventing seizures and the tendency to chronic invalidism."

The management regimen should include:[1]

I. Good physical and mental hygiene.
   a) Wholesome diet; Regular bowel habits; Avoid noxious materials, e.g. alcoholics; Moderate physical activity.
   b) Help overcome feeling that epilepsy is shameful; Encourage normal work and recreation; Regular sleep without overprotection.

II. Anticonvulsant medication selected on the basis of Exact Diagnosis:
   "Certain drugs are more effective in one type of seizure than they are in another, and it is necessary to use proper drugs. The dosage must be individualized for each case."[1]

Thus, the best guide in selecting medication for a patient is the type of seizures present. (Frequently several drugs in combination is most effective.)

The table shows which drugs are indicated for each type of seizure. It will be noted that the newer hydantoin, Mesantoin, is effective for *grand mal*, Jacksonian and focal seizures.

MESANTOIN DOSAGE is adjusted to the lowest level adequate to attain freedom from seizures. Start with ½ or 1 tablet daily during the first week; increase the daily intake by ½ or 1 tablet during the next week. Continue this up to optimal dosage. When another drug has not given good results, Mesantoin is added by the same procedure; then the old drug is gradually reduced.

SIDE EFFECTS — Mesantoin produces side effects in some cases: Skin and blood changes are signs of sensitivity — the drug should be discontinued. Drowsiness develops upon reaching maximum dosage.

PRECAUTIONS — Certain precautions are necessary to minimize untoward effects.

a. close check on patient — repeated visits and blood counts.
b. No Mesantoin, if white cell count below 4000.
c. caution if (1) rash or blood changes.
   (2) History of drug sensitivity.
d. discontinue drug if (1) bleeding of gums or vagina.
   (2) Sore throat

TYPE OF EPILEPSY	PRIMARY CLINICAL MANIFESTATIONS	MEDICATION	AVERAGE ADULT DAILY DOSE★	LIMITING SIDE EFFECTS	SIGNS OF SENSITIVITY
GRAND MAL	Aura followed by loss of consciousness; tonic-clonic convulsions and autonomic disturbance, e.g., in bladder function.	Phenobarbital	1¼ grs. h.s. Usual max.: 3 grs. per day	Sleepiness	
		5,5 diphenyl hydantoin	1½ grs. t.i.d., p.c. Usual max. 6 grs. per day	Diplopia, staggering (may increase petit mal)	Overgrowth of gums, body hairs; itching rash on extremities, gastric irritation
JACKSONIAN	Convulsions begin in one area and spread outwards (Jacksonian march.). No loss of consciousness.[2]	3 methyl 5,5 phenylethyl hydantoin (mesantoin)	Adults: 2 to 6 tabs. Children: 1 to 4 tabs.	Sleepiness	Full details given; see Psychomotor cross-column below
		phenylacetylurea[3]	2 Gms. per day. Max. dose 6 Gms. per day[4]	Drowsiness[5]	Central nervous system affected, nausea, vomiting and abdominal pain[5]
PSYCHO MOTOR	Period of amnesia; actions apparently purposeful but mechanical; incoordination. Mild tonic spasms. In children: "behavior problems".[2]	3 methyl 5,5 phenylethyl hydantoin[4]	Adults: 2-6 tabs. Children: 1-4 tabs.	Pharyngitis, mucous membrane bleeding, lymphadenopathy, measles-like rash with itching and fever; in severe reaction: blood dyscrasia.	
		phenylacetylurea[3]	See phenylacetylurea—above		
PETIT MAL TRIAD	Attacks: in series (rapid succession), abrupt onset, few sec. duration; no aura nor impairment of consciousness. Rhythmic twitching (e.g. eyelids).	3,5,5 trimethyl oxazolidine 2,4 dione	0.9 to 1.2 Gms.	Inability to see in a bright light. Drowsiness	Hiccough, acneform rash, leukopenia
		N methyl derivative of phenobarbital	6 grs.	Sleepiness	

★Although an average daily dose can be stated for each of these drugs, to obtain best results it is necessary that the physician determine the dose required by each individual patient for maximum control of his seizures.

Bibliography: 1. Carter, S., in Conn, H.: Current Therapy 1949; Phila., Saunders Co., p. 495. 2. Kaufman, I.: Dis. Nerv. System *11:* 99, 1950. 3. Lennox W.: Science & Seizures, ed. 2, N.Y.C., Harper & Bros., 1946. 4. Harris, T. & Otto, J.: Texas J. Med. *43:* 328, 1947. 5. Little S. & McBryde, R.: Am. J. M. Sc. *219:* 494, 1950. (Except as otherwise indicated, the data tabulated is from: Gibbs, F.: Ann. Int. Med. *27:* 548, 1947.)

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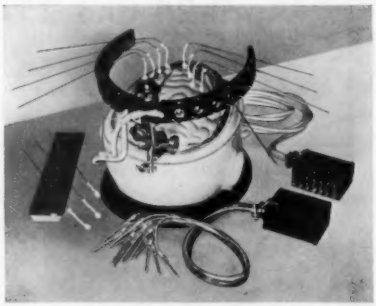

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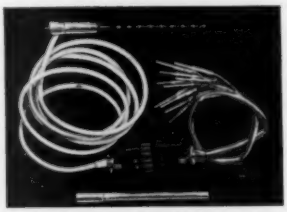

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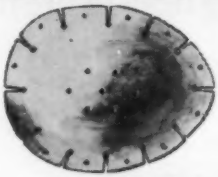

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Parenteral administration of Luminal Sodium promptly tones down nervous system excitement. Whether manifested as convulsions, psychic agitation, or pernicious vomiting, nervous overactivity is controlled profoundly and for prolonged periods with Luminal Sodium in adult doses of from 2 to 5 grains.

LUMINAL SODIUM is supplied in . . .

Hypodermic tablets of 65 mg. (1 grain), bottles of 50 and 500, for subcutaneous or intramuscular injection;

Powder, ampuls of 0.13 Gm. and 0.32 Gm. (2 grains and 5 grains), boxes of 5, 25 and 100, for subcutaneous, intramuscular and (exceptionally) intravenous injection;

Solution in propylene glycol, ampuls of 2 cc. (0.32 Gm. = 5 grains), boxes of 5 and 100, for intramuscular injection only.

Serrated ampuls. The constricted neck of Luminal Sodium powder ampuls is serrated for easy and clean opening. In making the file cut only moderate pressure is required.

LUMINAL® SODIUM

The Pioneer Brand of Phenobarbital Sodium

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